Chemotherapy: Antibiotics

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Introduction

- **Antibiotics** = a natural substance produced by a micro-organism to kill another
- **Anti-infectives/Anti-microbrial** = any agent (natural or synthetic) that kills pathogens (microbes)
- Kill the pathogens but not host cells.
  - Exploit the difference between them.

臨床上常見的致病微生物

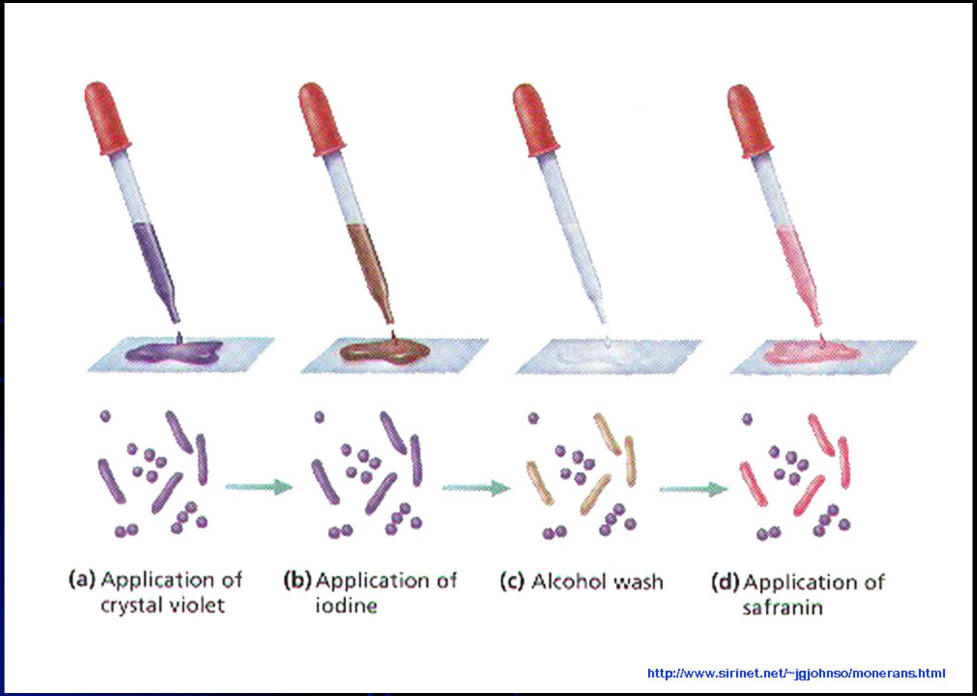
- Bacteria 細菌 — 最常見
- Mycoplasma 黴漿菌
- Fungi 黴菌
- Mycobacterium 結核菌
- Protozoa 寄生蟲
- Viruses 病毒

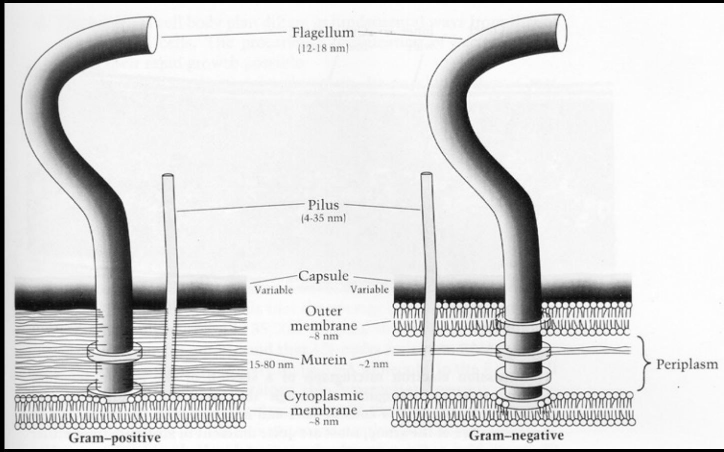
Classification of Bacteriae

- Gram (+) vs Gram (-)
- Bacilli vs cocci
- Aerobic vs anaerobic

Gram Stain: Principle & Practice

1884 Danish microbiologist **Christian Gram**





G(+) cell wall G(-)

Peptidoglycan (murein; 胞壁質) 9:1

臨床上常見的致病細菌

G- bacilli

Gram Negative
Bacilli
Cocci
Gram Positive

G- cocci

G+ bacilli

G+ cocci

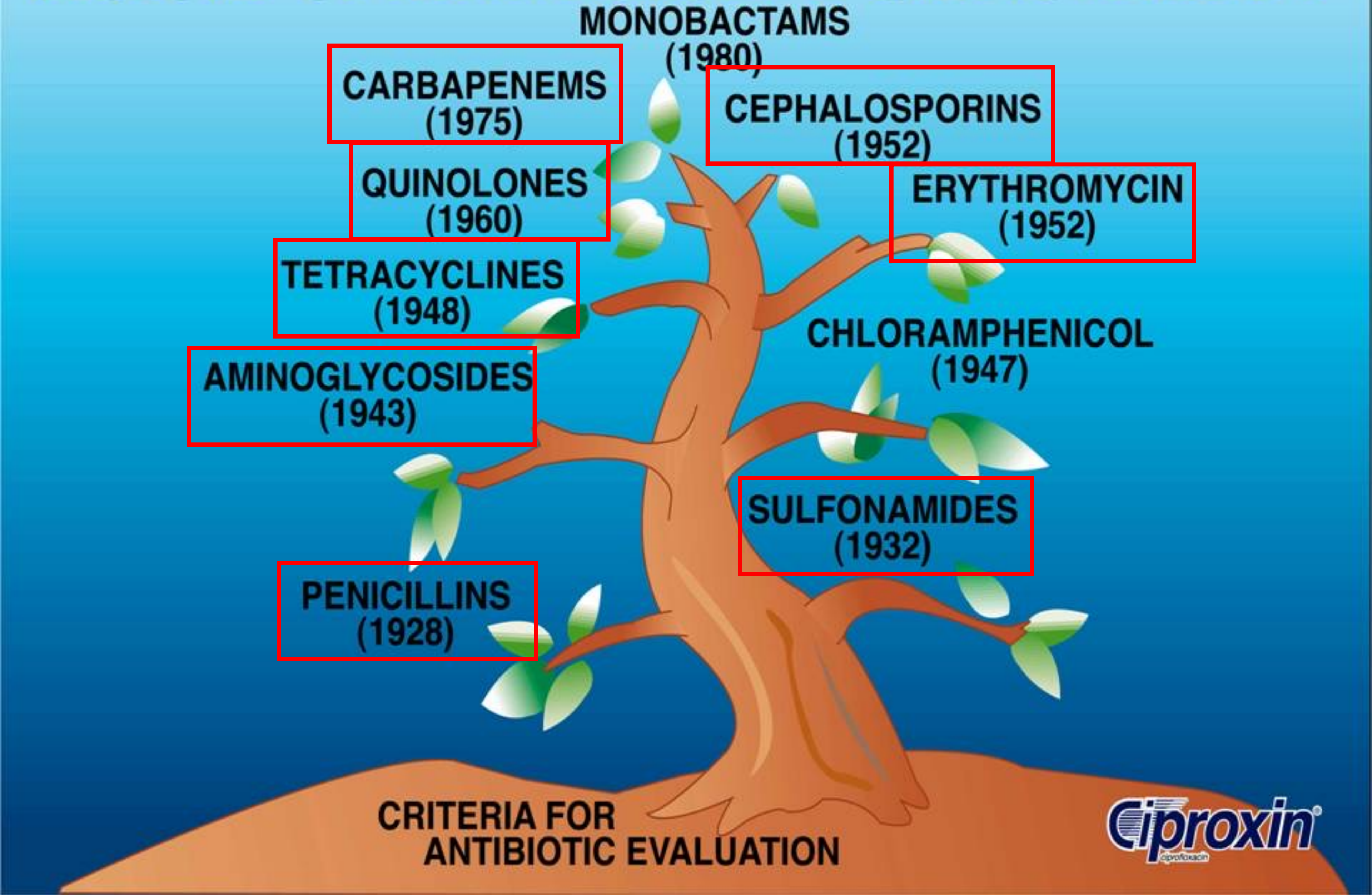
臨床上常見的致病菌

- Gram-positive bacteria
  - *Staphylococcus aureus*
  - Streptococcus
  - Enterococcus
- Gram-negative bacteria
  - *E. coli,* Klebsiella, Proteus
  - Enterobacter, Serratia
  - Non-fermentative Gram-negative bacilli (NFGNB)
  - *Haemophilus influenzae*
  - Meningococcus
- Anaerobic bacteria
  - *Bacteroides fragilis*
  - Others

History of Antibiotics

- Ancient Peru, Indians used bark from the cinchona tree (金雞納樹) to treat malaria
- Paul Ehrlich (Germany)
  - It would be possible to find chemicals that were selectively toxic for parasites but not toxic to humans --- "*magic bullet*"
- Fleming discovered penicillin G in 1929
- Gerhard Domagk in 1930s discovered sulfonamide
- Waksman in 1944 isolated streptomycin
  - Chloramphenicol, tetracyclines, erythromycin in soil
- 1960s, many new chemotherapeutic agents by molecular modification of existing compounds

HISTORY OF ANTIMICROBIAL CHEMOTHERAPY



Classification of Antibiotics

- Mechanism
- Structure

- Bacteriostatic, bacteriocidal
- Spectrum: broad vs narrow
  - Broad spectrum antibiotics – when the pathogen is unknown.
  - Narrow spectrum antibiotics – pathogen identified

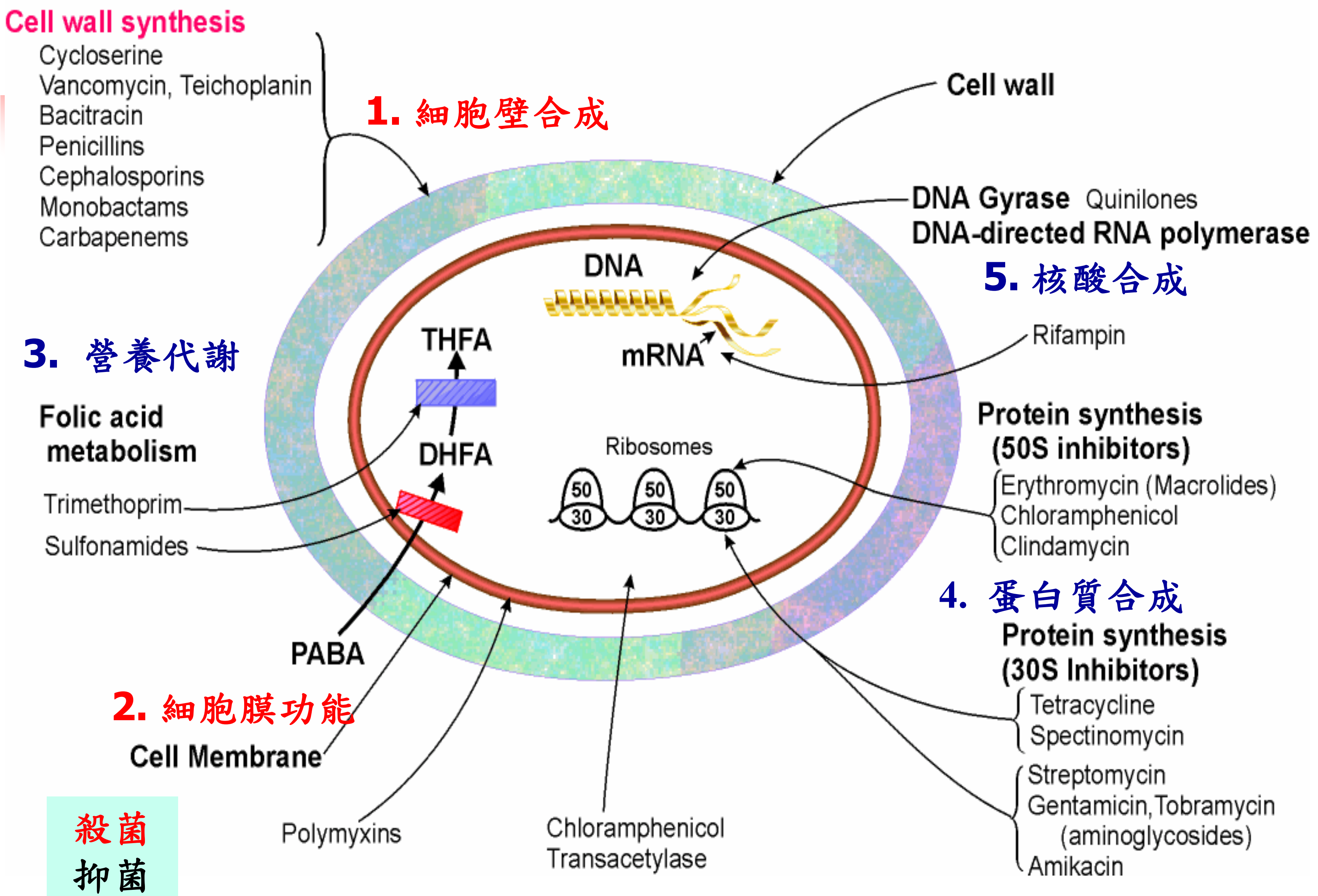
Mechanisms of Antimicrobial Agents

- Interfere with the synthesis of bacterial cell walls
  - Cell walls are not found in eucaryotic cells – highly selective.
  - Penicillins, cephalosporins, vancomycin, and bacitracin
- Inhibit protein synthesis by binding with ribosome.
  - Ribosomes are different in prokaryocytes. Moderately selective.
  - Affect different steps in protein synthesis: aminoacyl-tRNA binding, peptide bonds, mRNA reading, and translocation.
  - Streptomycin, gentamicin, spectinomycin, clindamycin, chloramphenicol, tetracyclines, erythromycin

Mechanisms of Antimicrobial Agents

- Inhibit nucleic acid synthesis or damage cell membranes
  - Usually not as selectively
- Metabolic antagonist
  - Sulfonamides (e.g., sulfanilamide, sulfamethoxazole, and sulfacetamide) are folate metabolsim inhibitors.
  - High therapeutic index because humans cannot synthesize folic acid. Yet most bacteriae synthesize folic acid.

Bacterial Targets for Current Antibiotics Used in the Clinic



殺菌
抑菌

Beta-lactam

Penicillin

Cephalosporin

Monobactam

~~Fluoroquinolone~~

Carbapenam

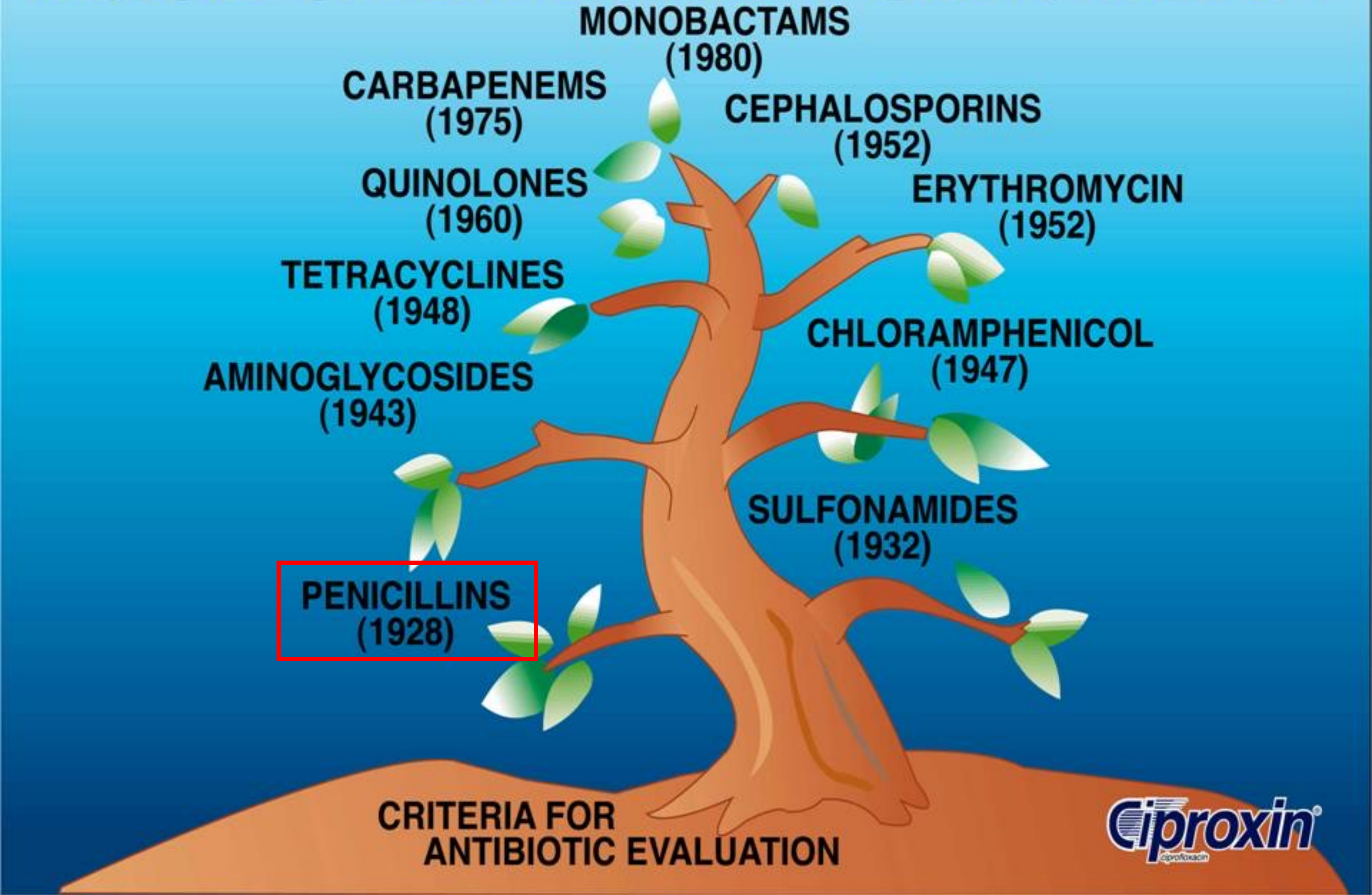
John

Paul

George

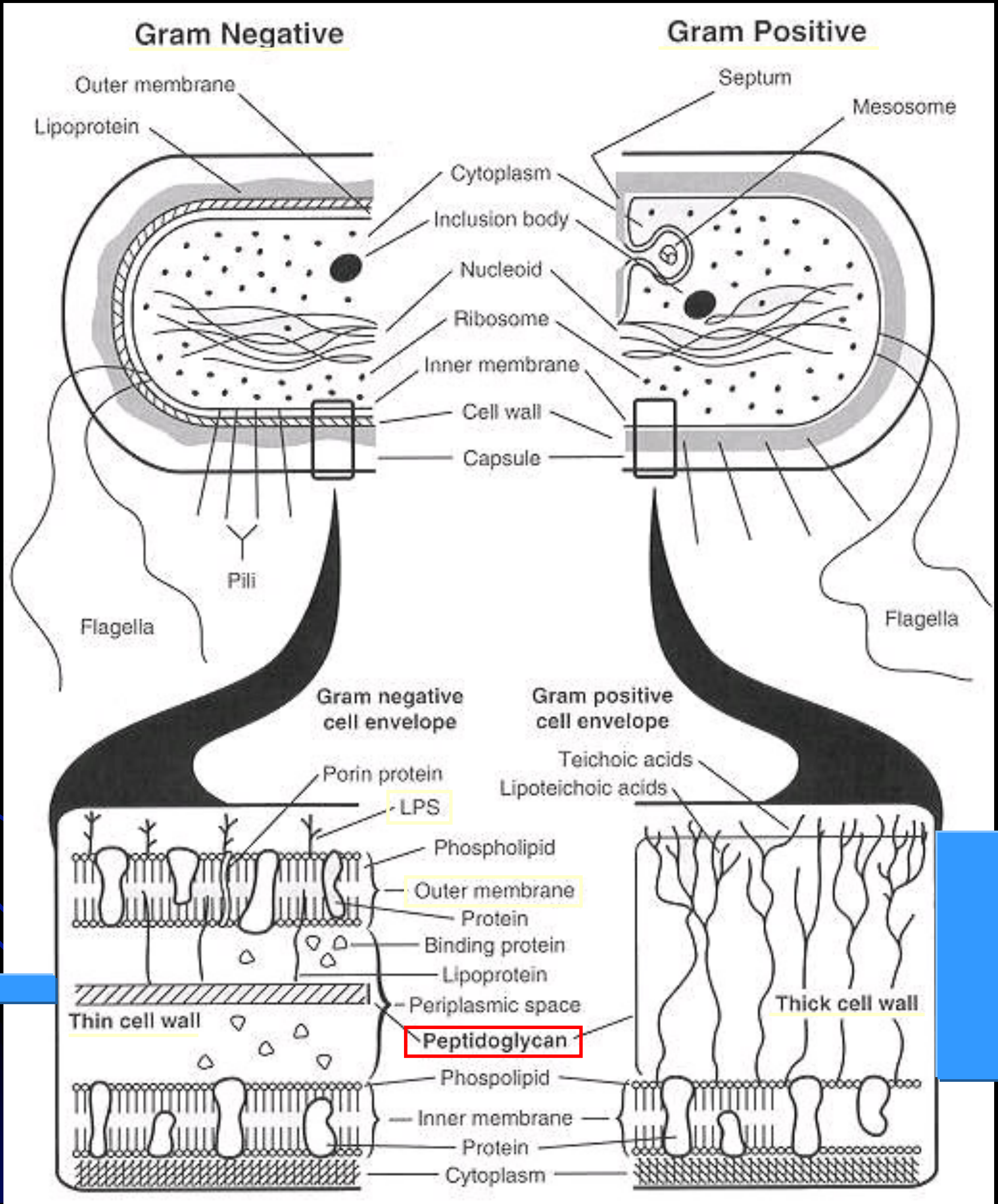
Ringo

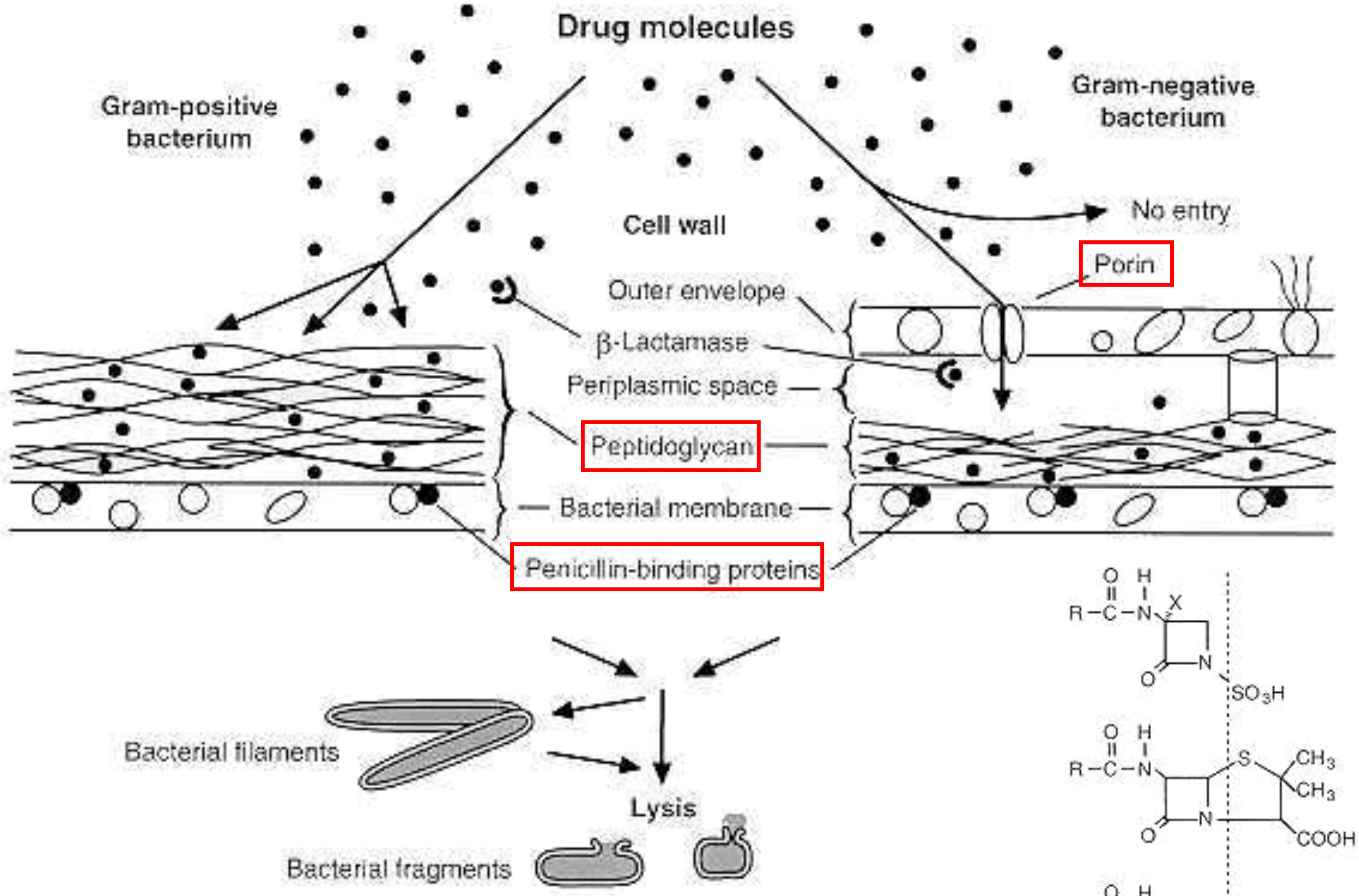
HISTORY OF ANTIMICROBIAL CHEMOTHERAPY

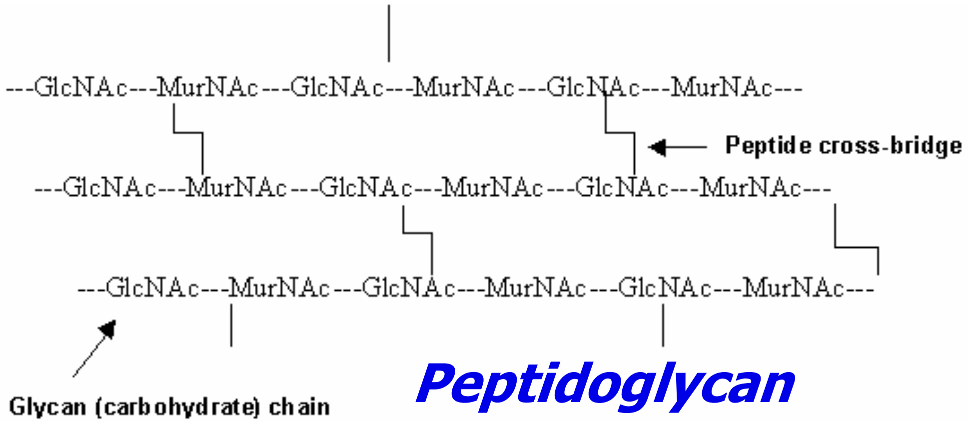


Mechanism of β-lactams

- Binding to penicillin-binding proteins (PBPs) located in bacterial cell walls
  - Inhibition of peptidoglycan synthesis
  - Bactericidal

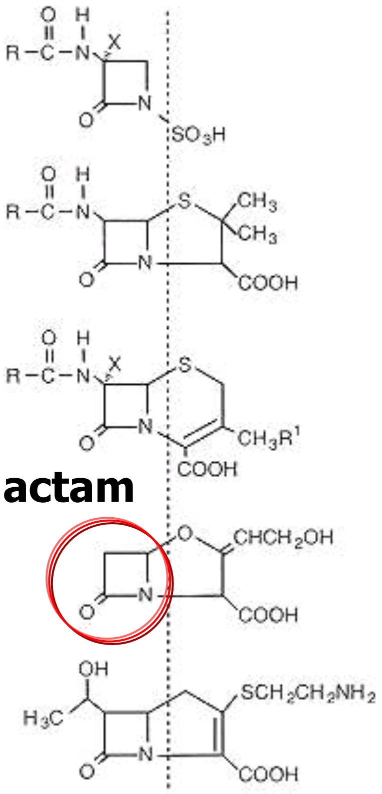

Gram Negative
Gram Positive
Outer membrane
Lipoprotein
Septum
Mesosome
Cytoplasm
Inclusion body
Nucleoid
Ribosome
Inner membrane
Cell wall
Capsule
Pili
Flagella
Flagella
Gram negative cell envelope
Gram positive cell envelope
Porin protein
LPS
Teichoic acids
Lipoteichoic acids
Phospholipid
Outer membrane
Protein
Binding protein
Lipoprotein
Periplasmic space
Thin cell wall
Thick cell wall
Peptidoglycan
Phospolipid
Inner membrane
Protein
Cytoplasm





Peptidoglycan

β-lactam



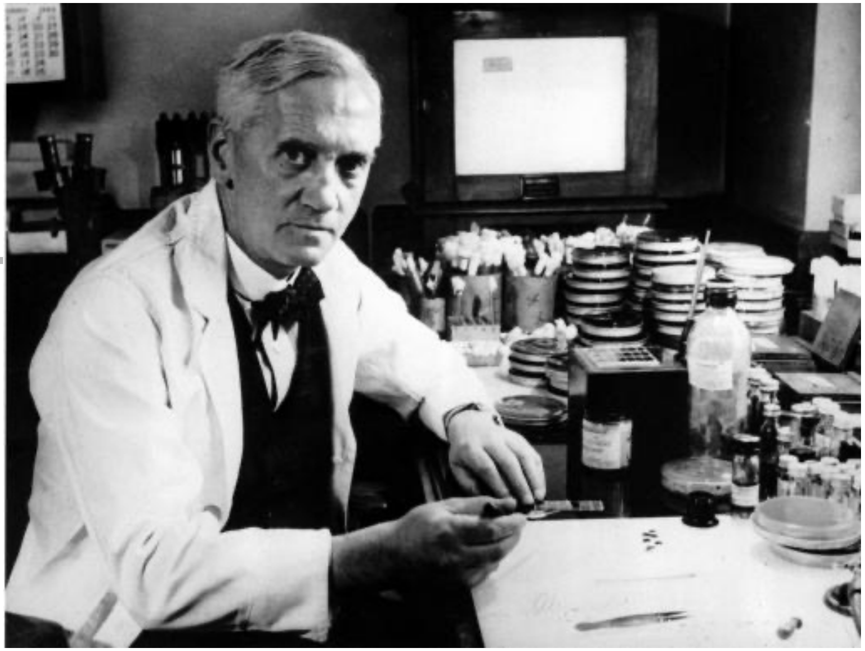
Monobactam

Penicillin

Cephalosporin
Cephamycin

Clavulanic acid

Thienamycin



PENICILLIN

Alexander Fleming discovers Penicillin 1928

A brilliant researcher, but quite careless lab technician …
stumbled upon penicillin thanks to his carelessness. …
a zone around fungus where bacteria could not grow

Classification of Penicillins

- Natural penicillins
  - Penicillin G (IV), Penicillin V (oral)
  - Effective: GPC, syphilis, actinomycosis, diphtheria, anthrax, Listeria, *Neisseria,* GP anaerobes above the diaphragm
  - Ineffective: Staphyloccus (penicillinase), GNB

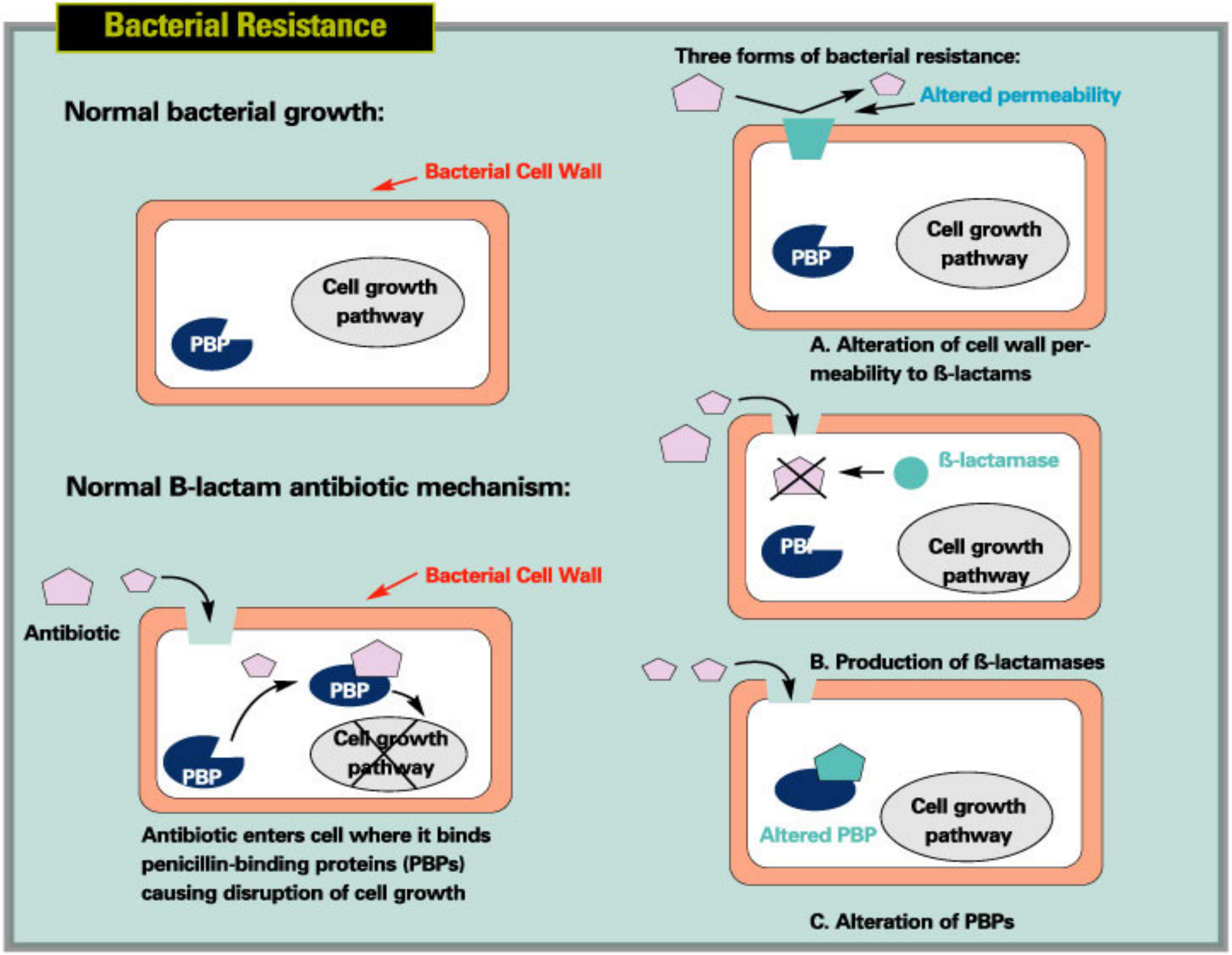
- Penicillinase-resistant penicillins
  - Oxacillin (IV) (Prostaphlin), Methicillin
  - For: Methicillin-sensitive Staphylococcus
  - Ineffective: MRSA, Enterococcus, GP anaerobes, GNB

Classification of Penicillins

- Aminopenicillin
  - Ampicillin (IV, oral), Amoxicillin (oral)
  - For GPC, *E. coli, K. pneumoniae, P. mirabilis, H. influenzae*
  - Ineffective: Staph, anaerobes, other GNB

- Anti-pseudomonal penicillins
  - Ureidopenicillin: Piperacillin (IV)
  - For GP anaerobes, GNB (*P. aeruginosa*, *Enterobacter.*, *Serratia,* some *Klebsiella sp.)*
  - Ineffective: Staph, H flu, Salmonella

Beta-lactam Resistance

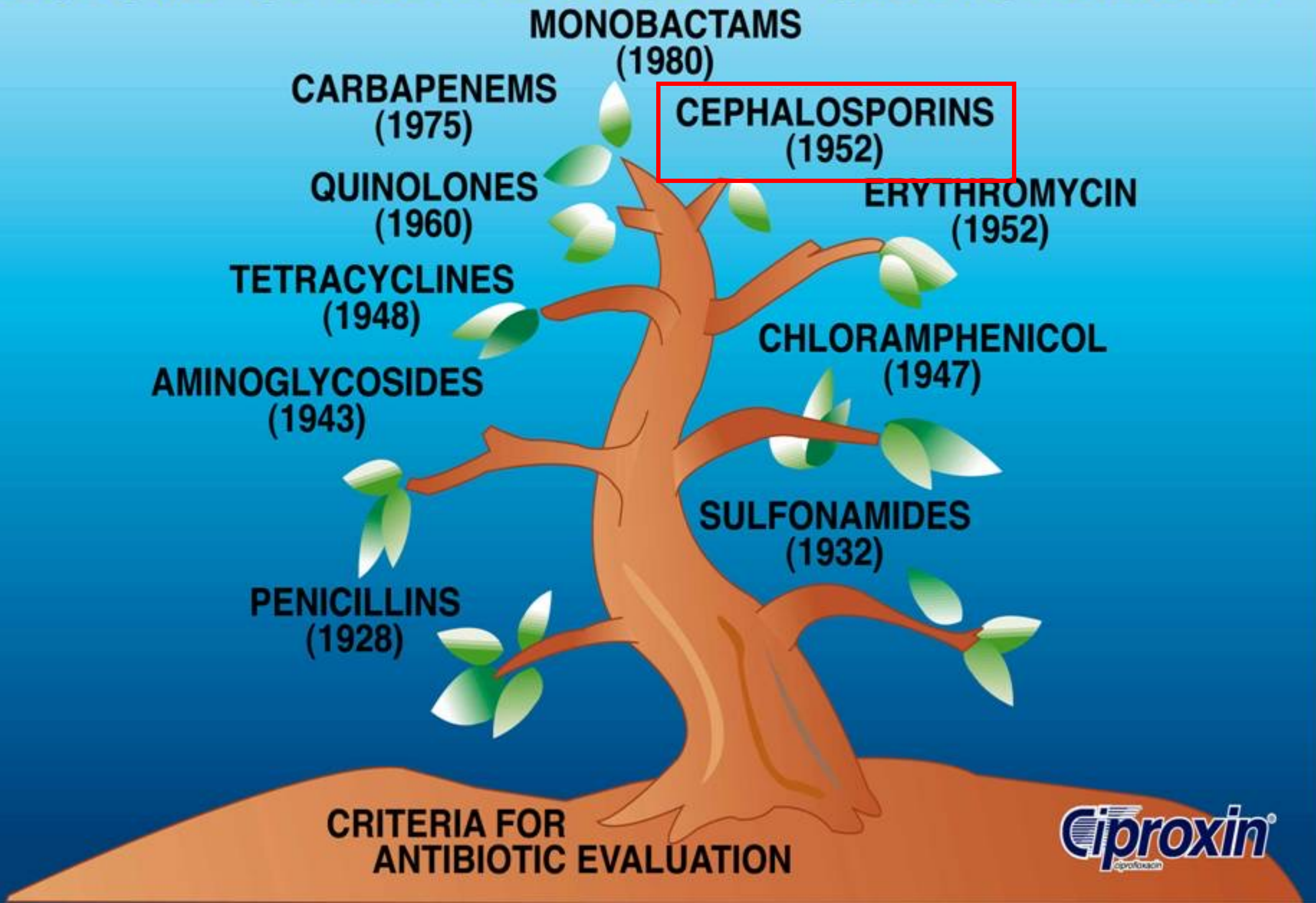


β-lactam/β-lactamase inhibitors

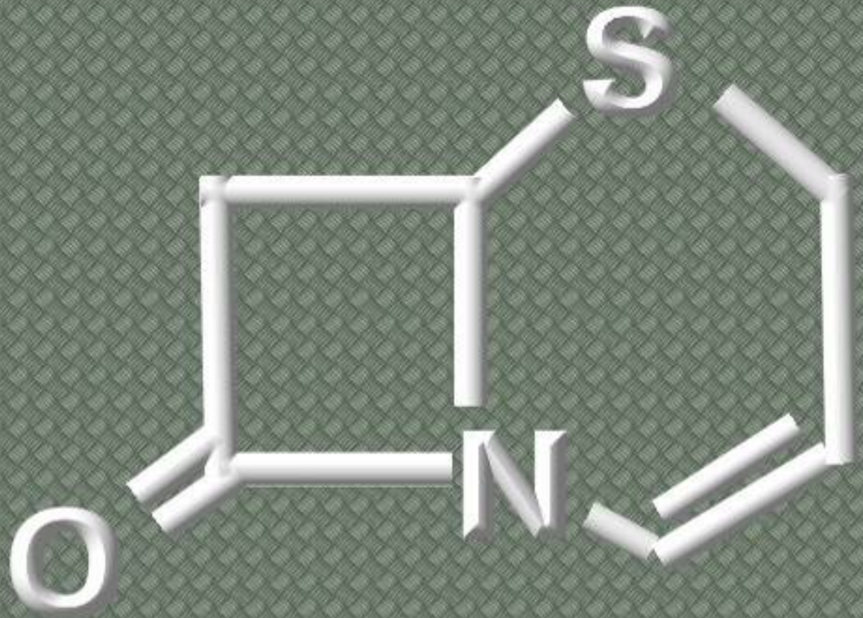
- Clinically used
  - Clavulanic acid
  - Sulbactam
  - Tazobactam

- β-lactam + β-lactamase inhibitor
  - Ampicillin + Sulbactam = Unasyn
  - Amoxicillin + Clavulanic acid = Augmentin
  - Ticarcillin + Clavulanic acid = Timentin
  - Piperacillin + Tazobactam = Tazocin

HISTORY OF ANTIMICROBIAL CHEMOTHERAPY



Cephalosporin



(Cephem)

Classification of Cephalosporins

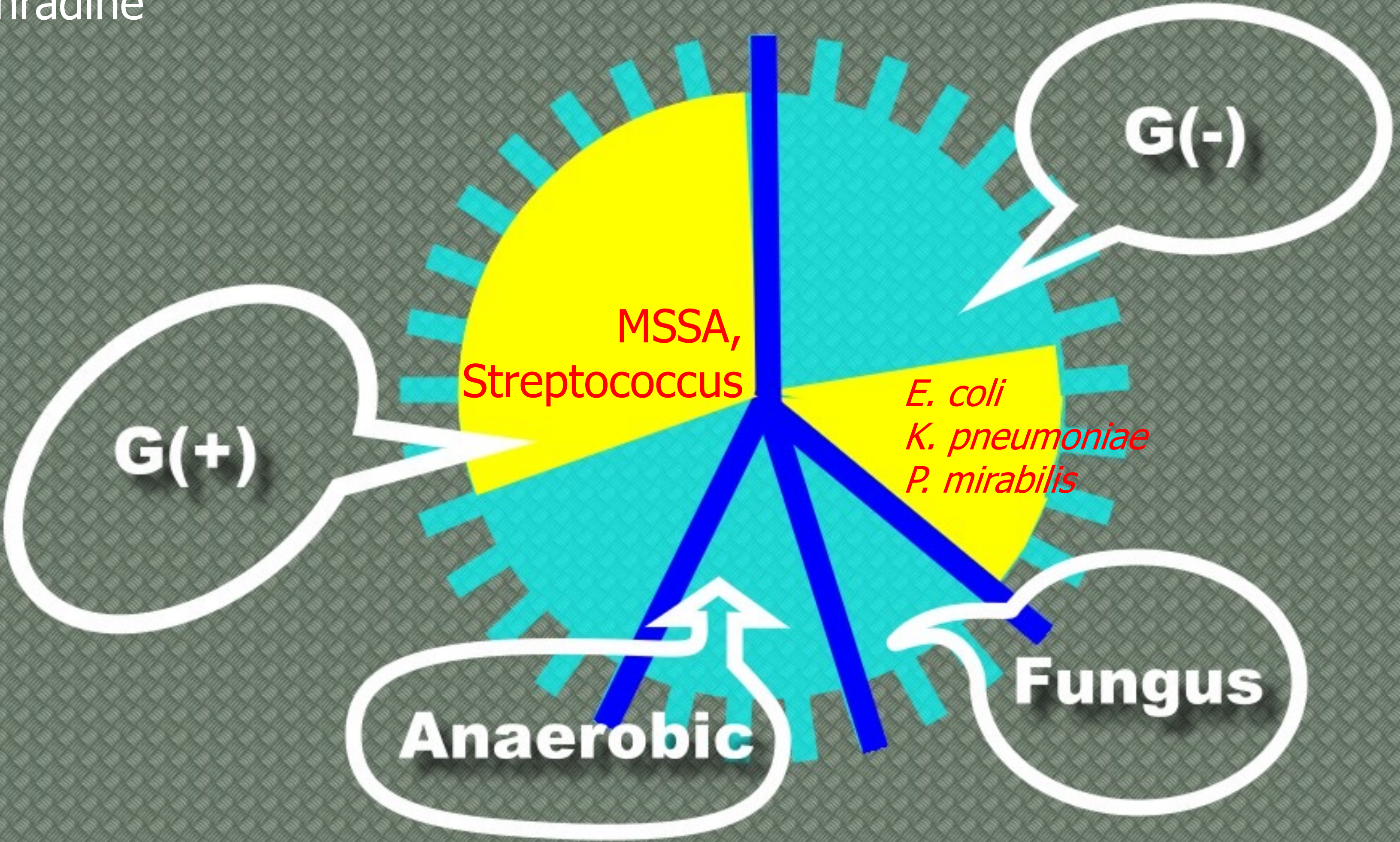
- Divided into 4 major groups called "Generations" based on
  - Antimicrobial activity
  - Resistance to beta-lactamase

Cephalosporin

- First-generation cephem
  - Cefazolin (IV), Cephalexin (oral)
- Second-generation cephem
  - Above diaphragm: Cefuroxime (IV, oral), Cefotiam(IV)
  - Below diaphragm: Cefoxitin, cefmetazole
- Third-generation cephem
  - Without antipseudomonal activity
  - With antipseudomonal activity
- Fourth-generation cephem
  - Cefepime, Cefpirome

1'Cephalosporin

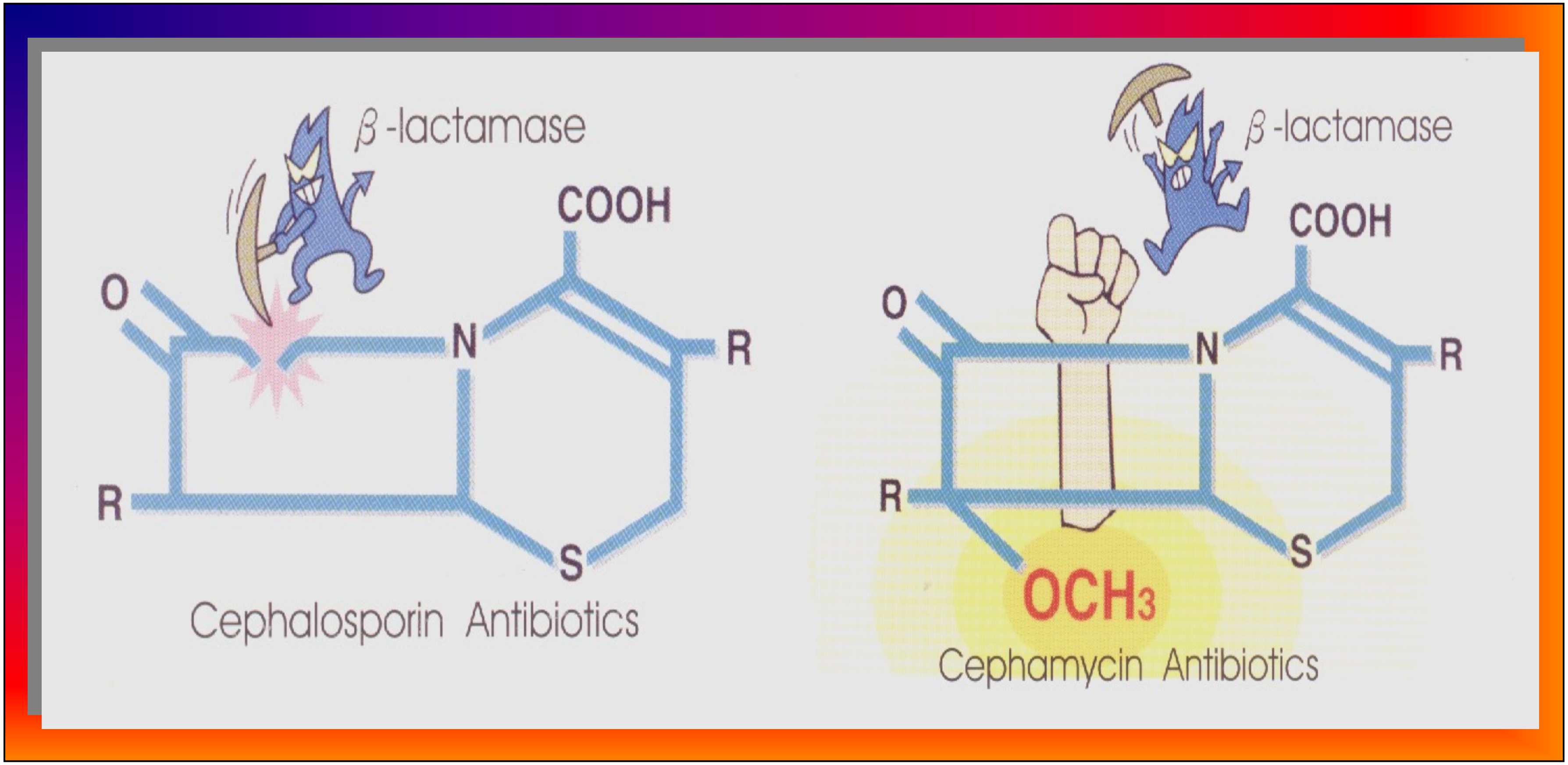
- **Cefazolin**
- Cephapirin
- Cephradine



Second-generation Cephalosporin

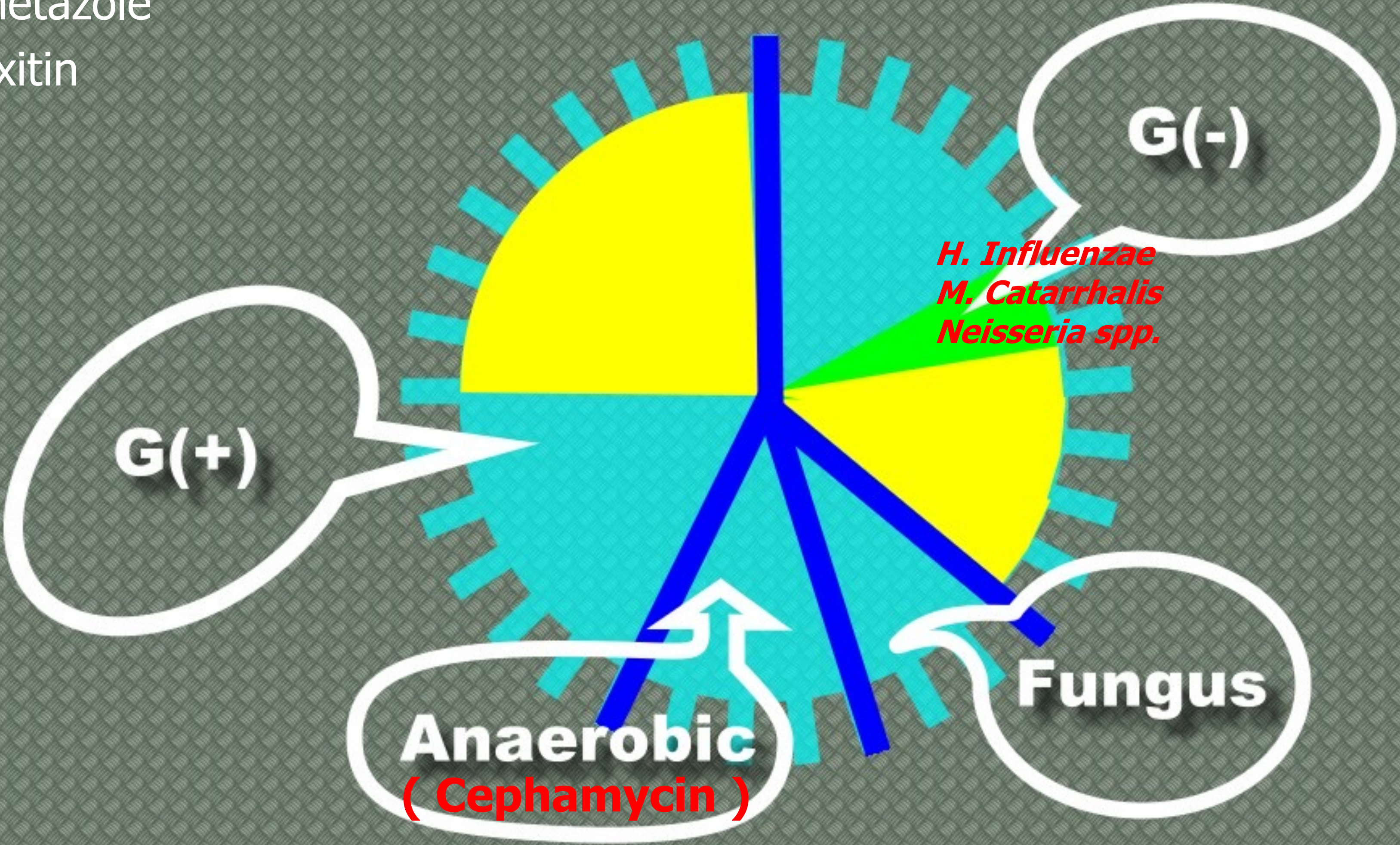
- True Cephalosporin:
  - Enhance the anti-GNB effect of 1st Cephalosporin
  - Less effective for GPC
  - Cefuroxime (Zinacef IV, Zinnat PO), Cefotiam (Pansporin), Cefaclor (Keflor)
- Cephamycins:
  - Cefmetazole (Cefmetazon), Cefoxitin (Mefoxin)
  - With the effect for anaerobes: *Bacteroides fragilis* group
- Ineffective:
  - MRSA, Enterococcus, other GNB

Cephalosporin VS Cephamycin



2'Cephalosporin

- Cefuroxime
- Cefotiam
- Cefmetazole
- Cefoxitin

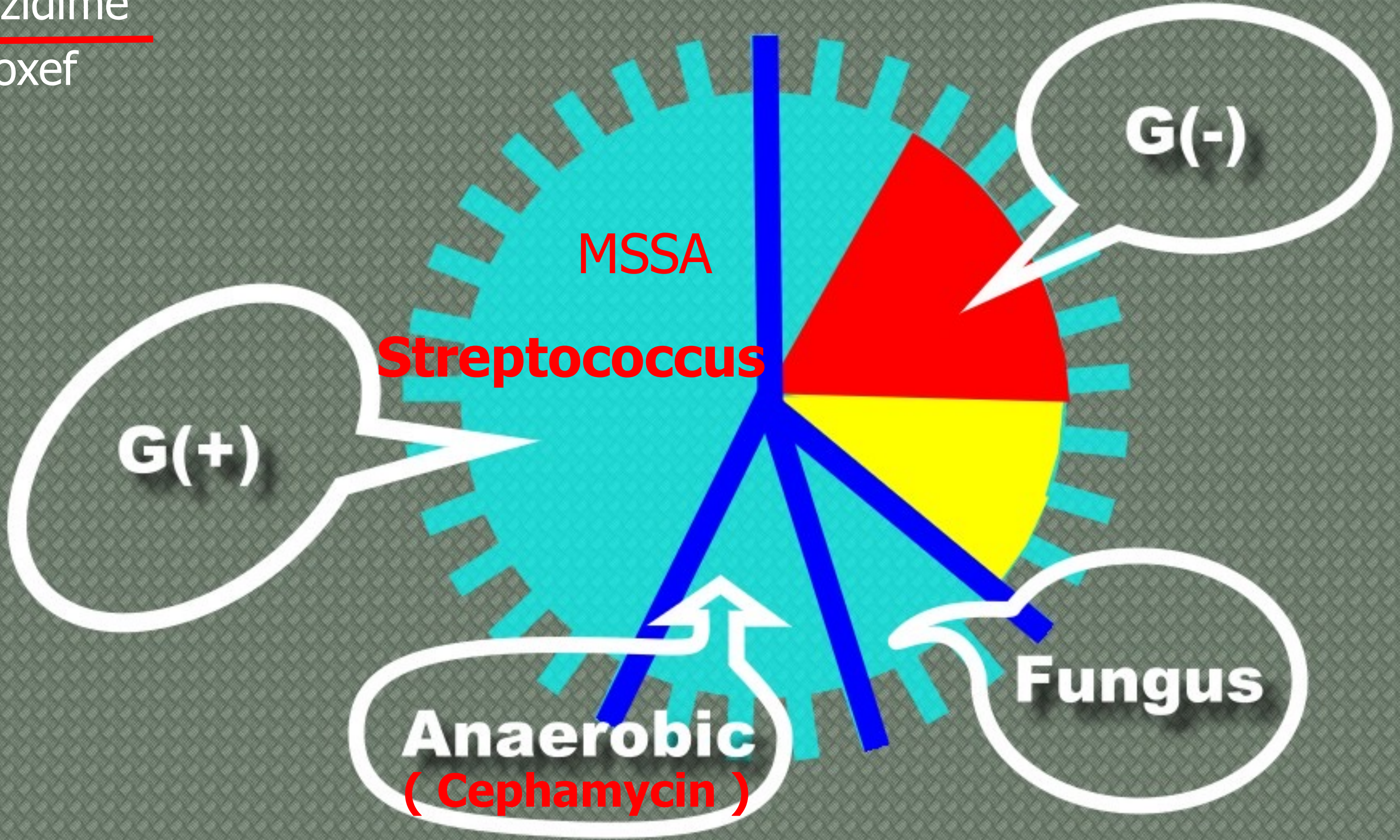


Third-generation Cephalosporin

- Activity:
  - Enhanced activity for streptococcus
  - Strong effect for Enterobactereacea
  - Ceftazidime is effective for *P. aeruginosa*
- True cephem:
  - Cefotaxime (Claforan), Ceftriaxone (Rocephin), Ceftazidime (Fortum)
- Cephamycin:
  - Flomoxef (Flumarin): effective for anaerobes and most MSSA

3'Cephalosporin

- Cefotaxime
- Ceftriaxone
- Ceftazidime
- Flomoxef

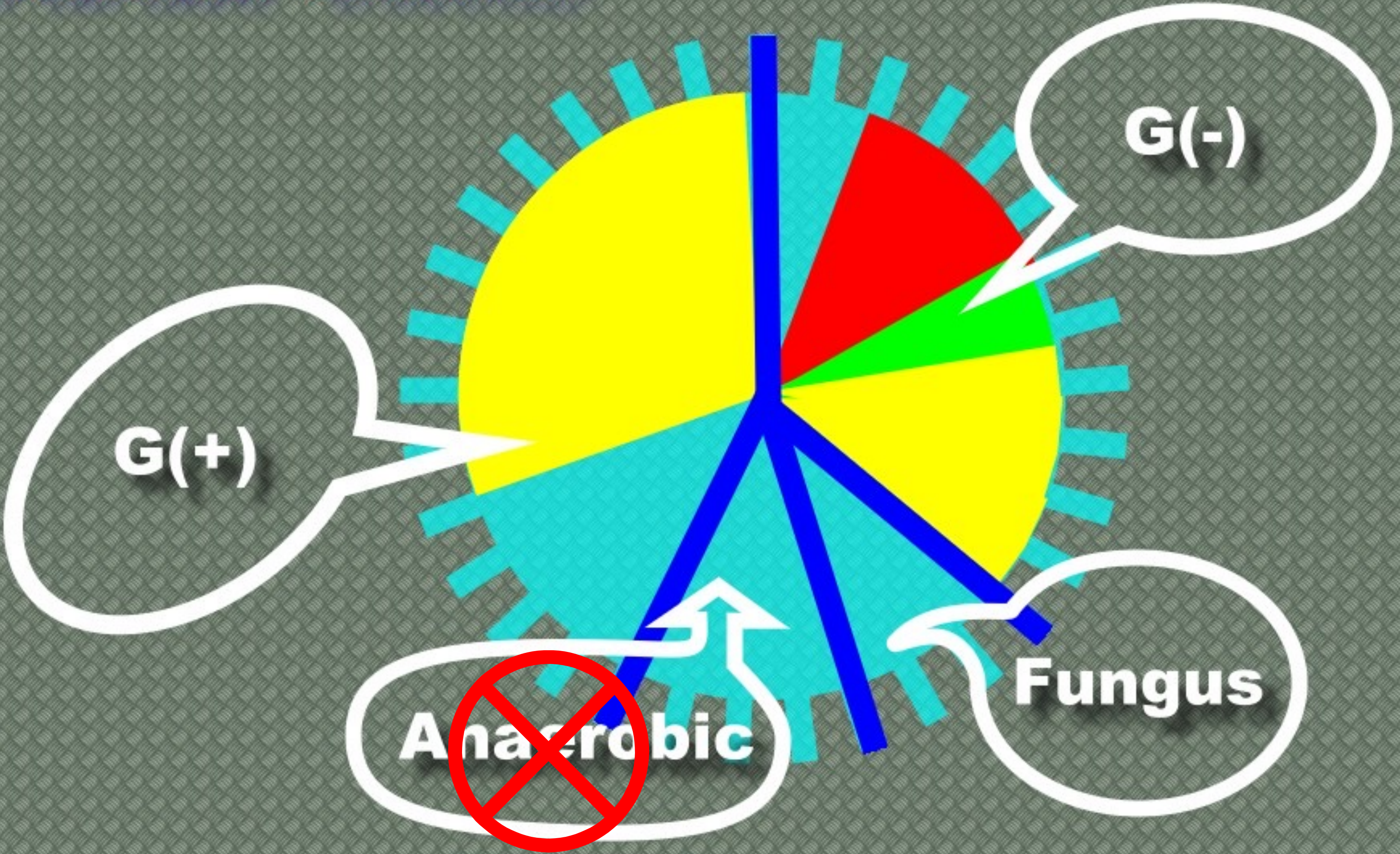


Fourth-generation Cephalosporin

- Activity:
  - Most MSSA, Streptococcus
  - Most enterobactereacea, including Enterobacter, Citrobacter, Serratia, Morganella
  - *Pseudomonas aeruginosa*
- Ineffective:
  - Enterococcus, MRSA
  - Anaerobes
- Cefepime (Maxipime), Cefpirome (Cefrom)
- Poor inducer of ESBL

4'Cephalosporin

MAXIPIME



Spectrum of Cephalosporin

	1° cephem	2° cephalosporin	2° cephamycin	3° cephem	4° cephem
Gram (+)					
Staph MSSA	+++	+	+	-	+
MRSA	-	-	-	-	-
Streptococcus	++	++	++	+++	+++
Enterococcus	-	-	-	-	-
Gram (-)					
E. coli, Kleb	-~++	++	++	+++	+++
Enterobacteriaceae	-	-	-	+	+~++
Pseudomonas	-	-	-	-	+++
Haemophilus	-	++	++	+++	+++
Anaerobic					
Bacteroides	-	-	++	-	-

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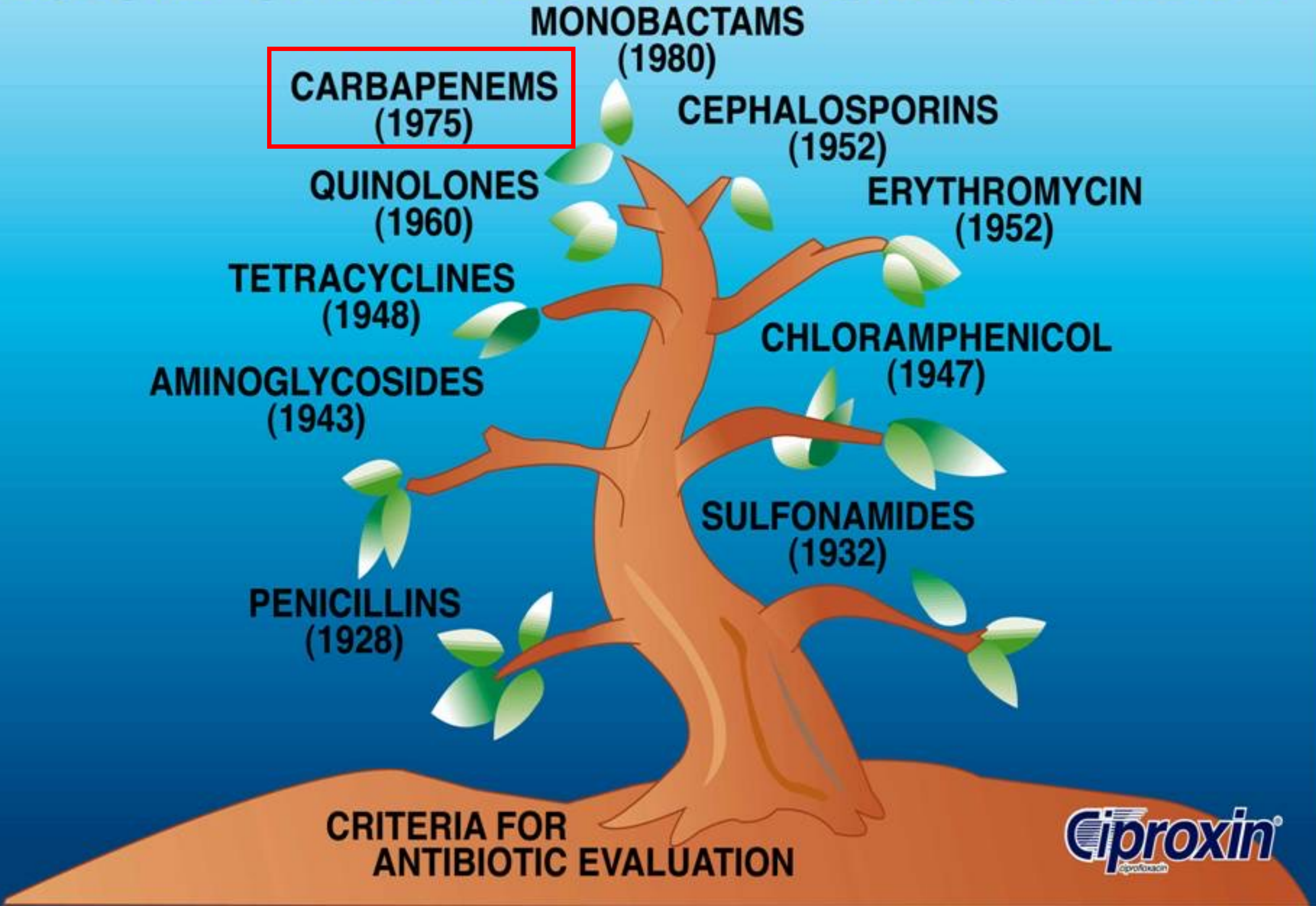
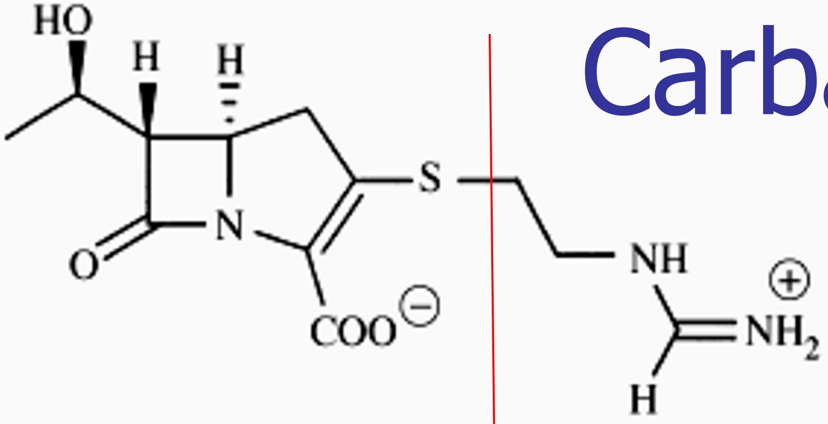
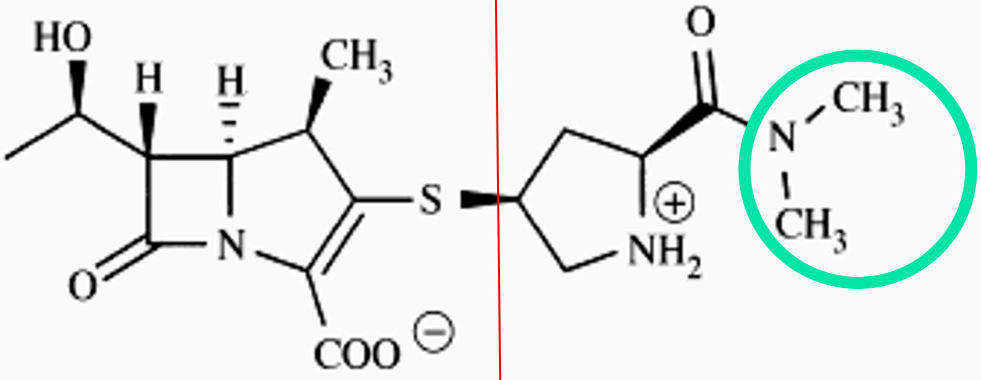


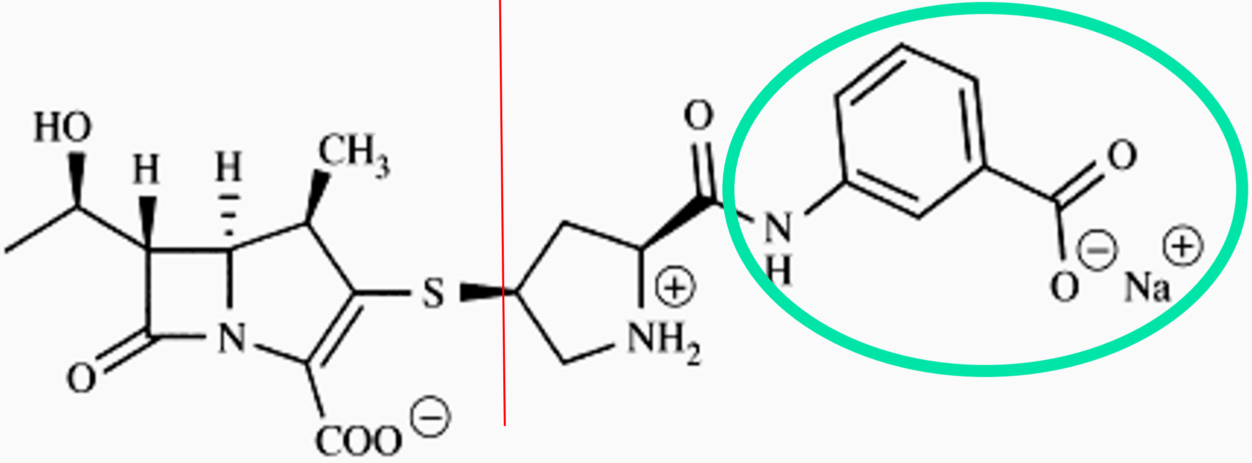
Carbapenems



Imipenem
Plasma protein binding = 20%
Molecular weight:317.37



Meropenem
Plasma protein binding = 2%
Molecular weight: 437.52



$T_{1/2}$ 4hrs, once daily

Ertapenem
Plasma protein binding = ~ 94%
Molecular weight: 497.50

Carbapenem

- Thienamycin (1970) (*Streptomyces cattleya*)
- Imipenem (N-formimidoyl) (1977)
- Meropenem (1984)
- Ertapenem (1989)

Carbapenem classification

Group	Classification
Group 1	Broad-spectrum carbapenems, *with limited activity against non-fermentative Gram-negative bacilli (e.g. Pseudomonas, Acinetobacter)* , that are particularly suitable for community-acquired infections (e.g. ertapenem)
Group 2	Broad-spectrum carbapenems, *with activity against non-fermentative Gram-negative bacilli (e.g. Pseudomonas, Acinetobacter*), that are particularly suitable for nosocomial infections (e.g. imipenem and meropenem)
Group 3	Carbapenems with clinical activity against Methicillin-Resistant *Staphylococcus* (e.g. In development)

J Antimicrob Chemotherapy DOI:10, 1093/jac/dkg 404

Spectrum of activity

- Gram(-): Invanz ≈ Mepem > Tienam
- Gram(+): Tienam > Invanz ≈ Mepem
- Anaerobes: Mepem ≧ Tienam ≧ Invanz

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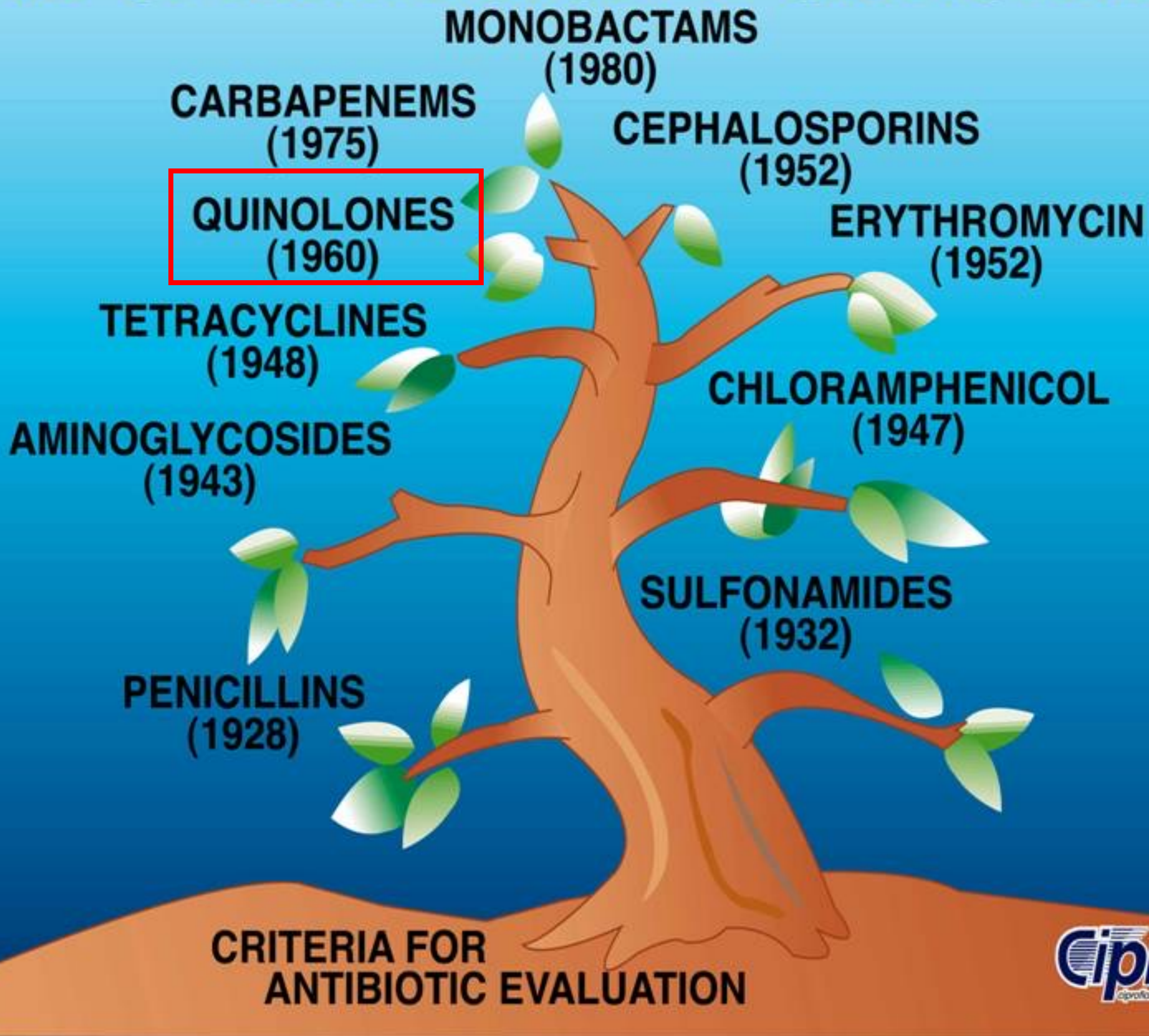
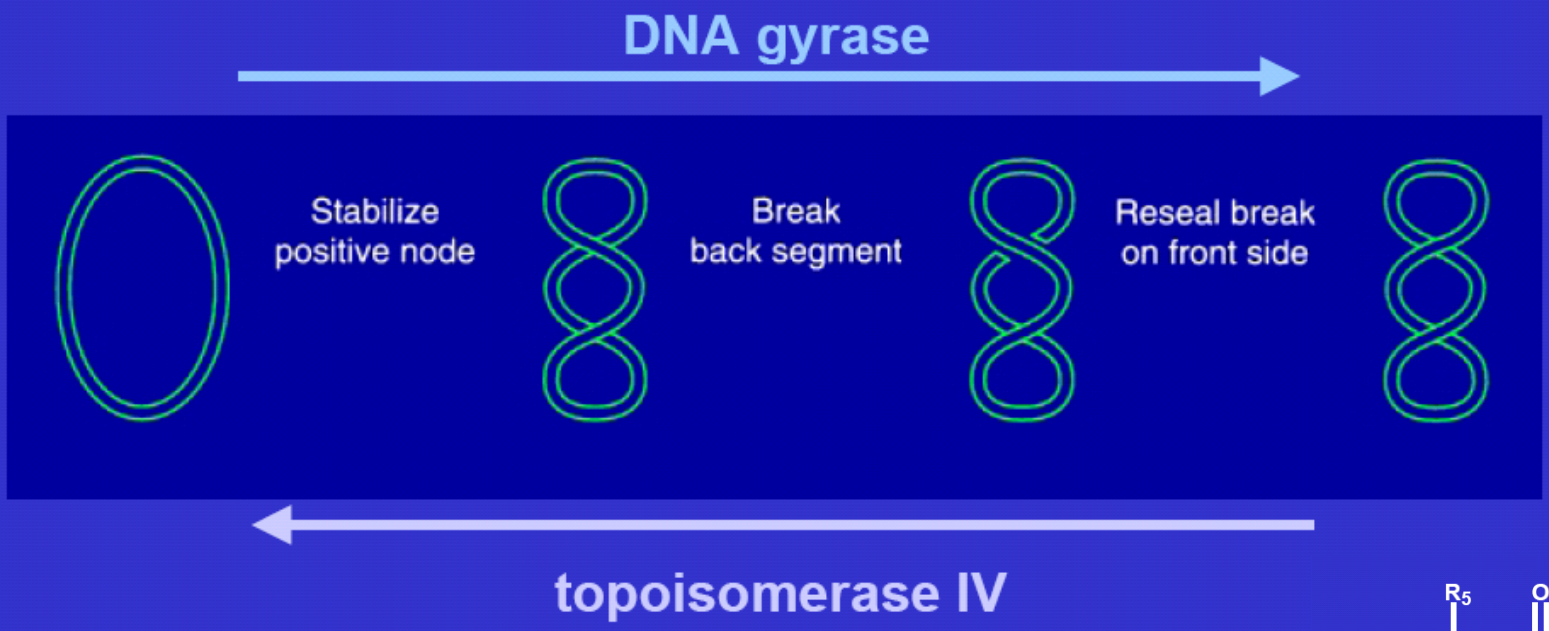


Ciproxin

Quinolones

- First entirely man-made antibiotics
- By-product of chloroquine (anti-malaria)

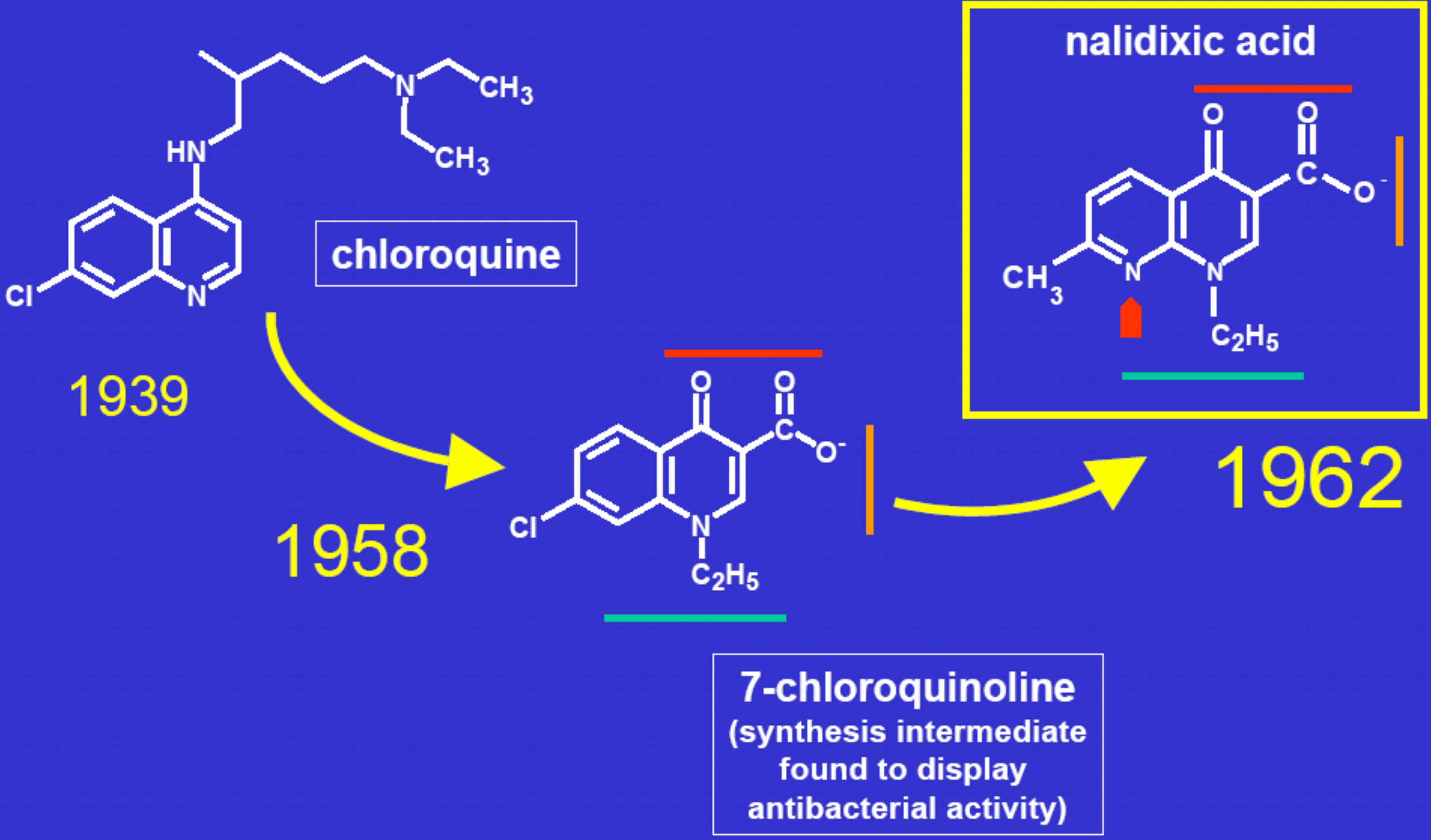


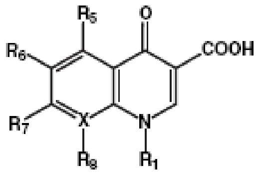
bacterial DNA is supercoiled

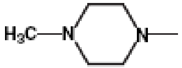
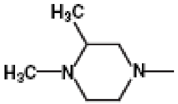
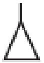
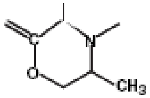
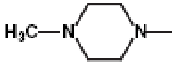
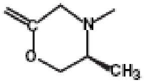
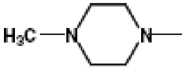
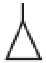
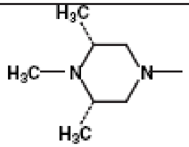
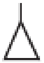
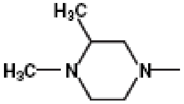
Mechanism

- DNA gyrase (Topoisomerase II)– removes excess positive supercoiling in the DNA helix
  - Primary target: G(-) bacteria
- Topoisomerase IV – essential for separation of interlinked daughter DNA molecules
  - Primary target : G(+) bacteria

From chloroquine to nalidixic acid





generation	drug [orig. ref./patent]]	X	R8	R1	R5	R6	R7
1	nalidixic acid [283;284]	N		$-CH_2-CH_3$	H	H	$-CH_3$
2a	**norfloxacin** [285-287	C	H	$-CH_2-CH_3$	H	F	
	pefloxacin [288;289]	C	H	$-CH_2-CH_3$	H	F	
	lomefloxacin [290;291]	C	F	$-CH_2-CH_3$	H	F	
	ciprofloxacin [292-294]	C	H		H	F	
	ofloxacin [295;296]				H	F	
	levofloxacin [297;298]				H	F	
2b	*sparfloxacin* [299;300]	C	F		$-NH_2$	F	
	grepafloxacin [301;302]	C	H		$-CH_3$	F	

1st Generation:
Narrow spectrum, low serum levels and toxicity issues

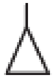
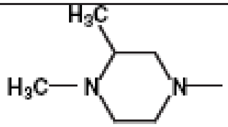
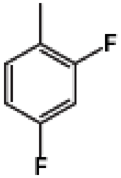
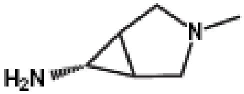
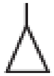
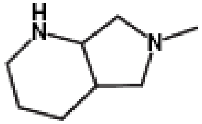
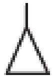
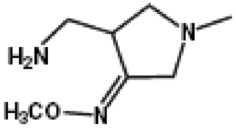
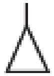
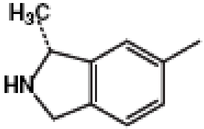
2nd generation:

Most potent against GNB

Marginal effect to *streptococcus*

Emergent resistance to *staphylococcus aureus*

Clinical Microbiology & Infection 11(4):256-280, 2005

3a	gatifloxacin [303;304]	C	-O-CH_3		H	F	
	trovafloxacin [305;306]	N			H	F	
	moxifloxacin [307;308]	C	-O-CH_3		H	F	
3b	gemifloxacin [309;310]	N			H	F	
4	garenoxacin [311;312]	C	-O-CHF_2		H	H	

3rd generation:

Improvement in GPC

Anti-anaerobe activity

Clinical Microbiology & Infection 11(4):256-280, 2005

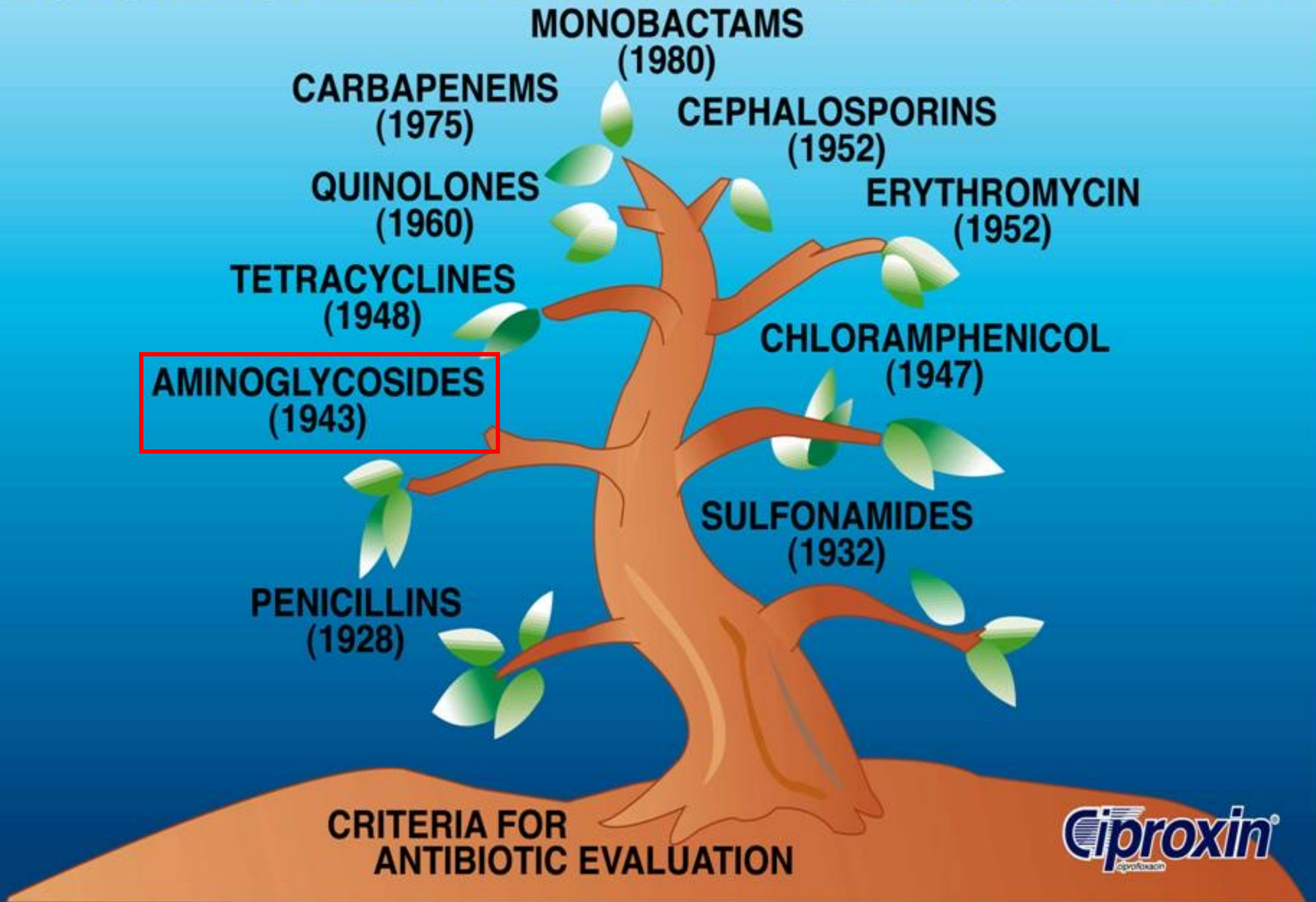
Fluoroquinolone

Pathogen	GNB	NFGNB	GPC	Atypical	Anaerobic
1st generation	+	-	-	-	-
2nd generation	++	++	-	+	-
3rd generation	++	+	+	++	+
4th generation	++	++	++	++	+

Special consideration

- One step mutation results in resistance
- Cross resistance is a common phenomenon
- Al^{3+}, Mg^{2+}, Fe^{3+}, Ca^{2+}, Zn^{2+}, Antacids, Sucralfate, enteral feedings can markedly impair absorption of oral quinolones
- QT prolongation

HISTORY OF ANTIMICROBIAL CHEMOTHERAPY



Aminoglycosides

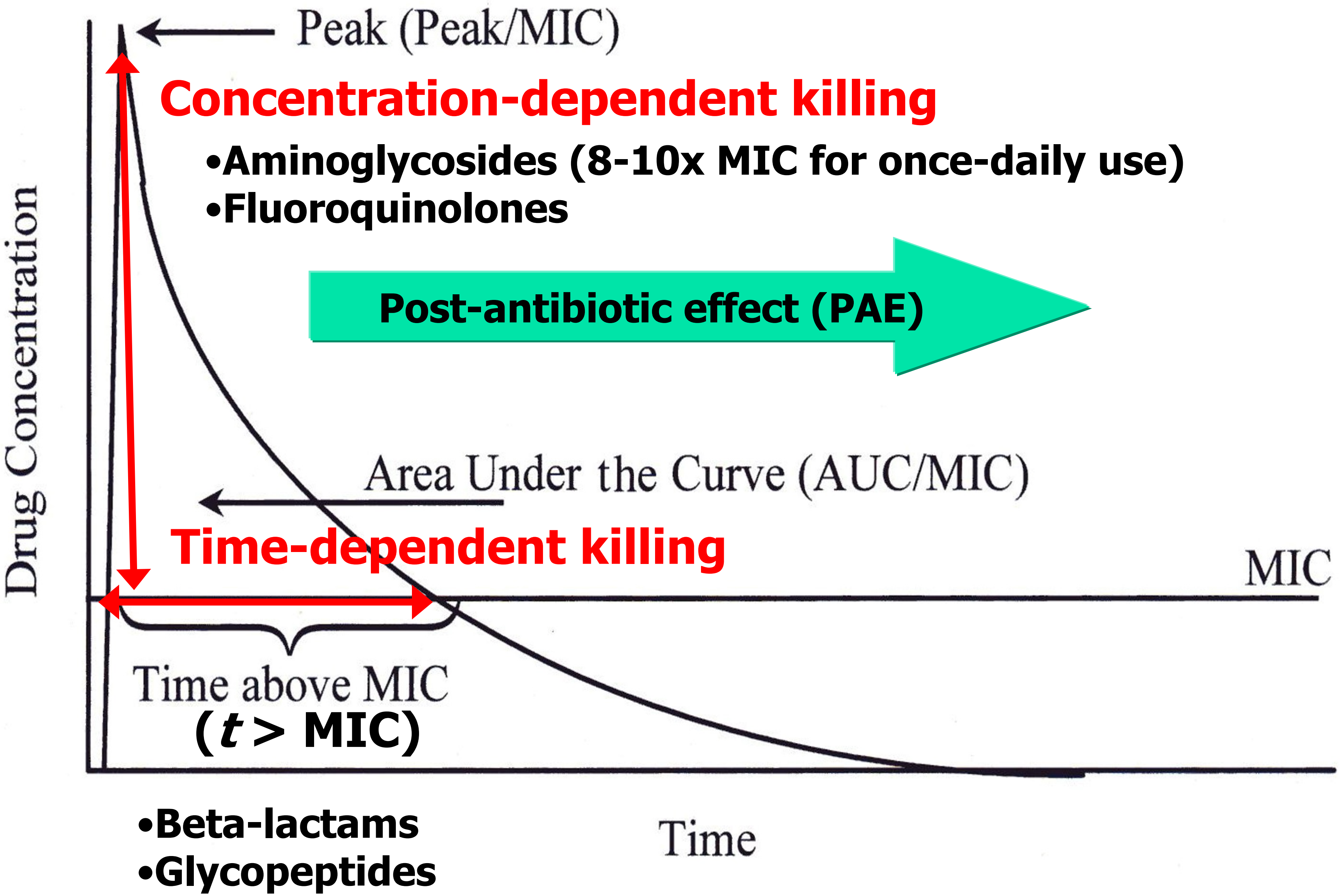
- Streptomycin
- Gentamicin
- Tobramycin
- Amikacin
- Netilmicin
- Kanamycin

- Anti-Gram-negative bacteria
  - Could be used alone, but seldom used alone
  - In combination with other antibiotics
    - β-lactam + aminoglycoside

Spectrum of Activity

- Activity:
  - Most bacteria
  - Mycobacteria
    - Tuberculosis - streptomycin
    - Atypical - streptomycin or amikacin
- Ineffective: *H. influenzae* & anaerobes
- Special consideration:
  - Not active in anaerobic and acidic area
  - Once daily regimen
  - Synergism with β–lactams

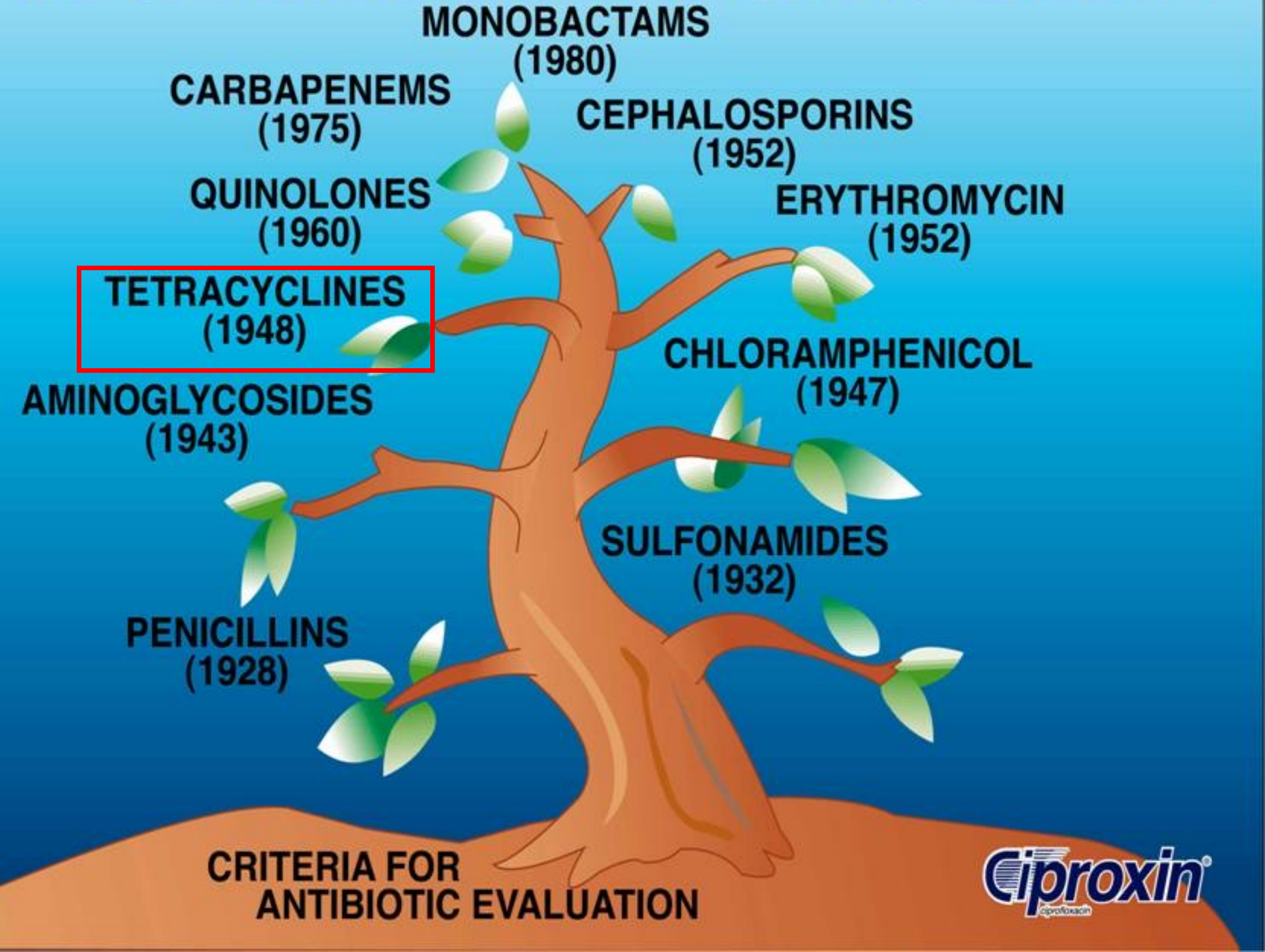
Pharmacodynamics: Dosing Strategies



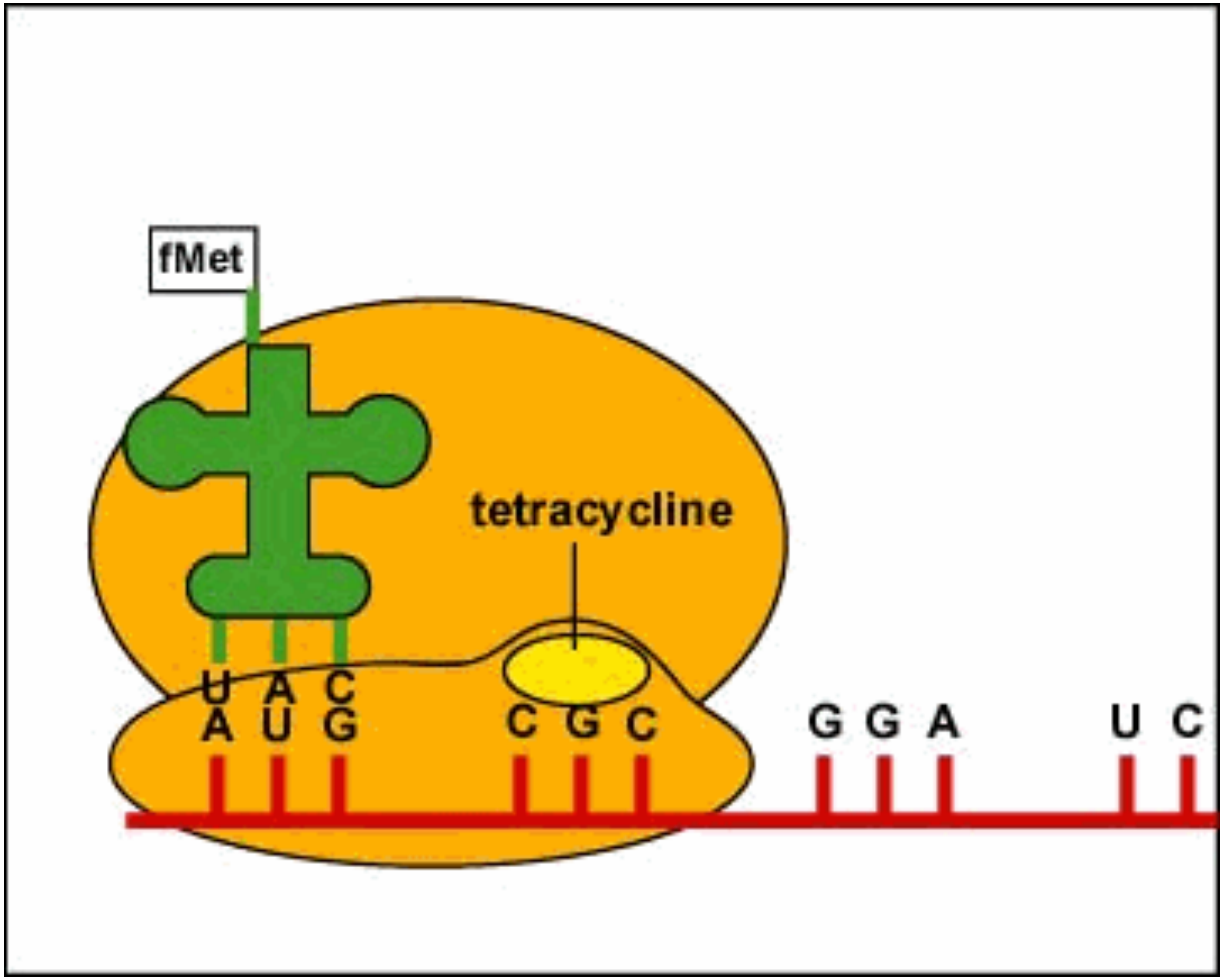
Duration Dependent vs. Concentration Dependent

- Time dependent (T>MIC):
  - β-lactams
  - Glycopeptides
  - Macrolides
  - Clindamycin
  - Oxazolidinone
- Concentration dependent (Cmax/MIC):
  - Aminoglycosides
  - Quinolones
  - Metronidazole
  - Daptomycin
  - Colistin
  - Amphotericin B

HISTORY OF ANTIMICROBIAL CHEMOTHERAPY



Tetracycline mechanism



Tetracyclines

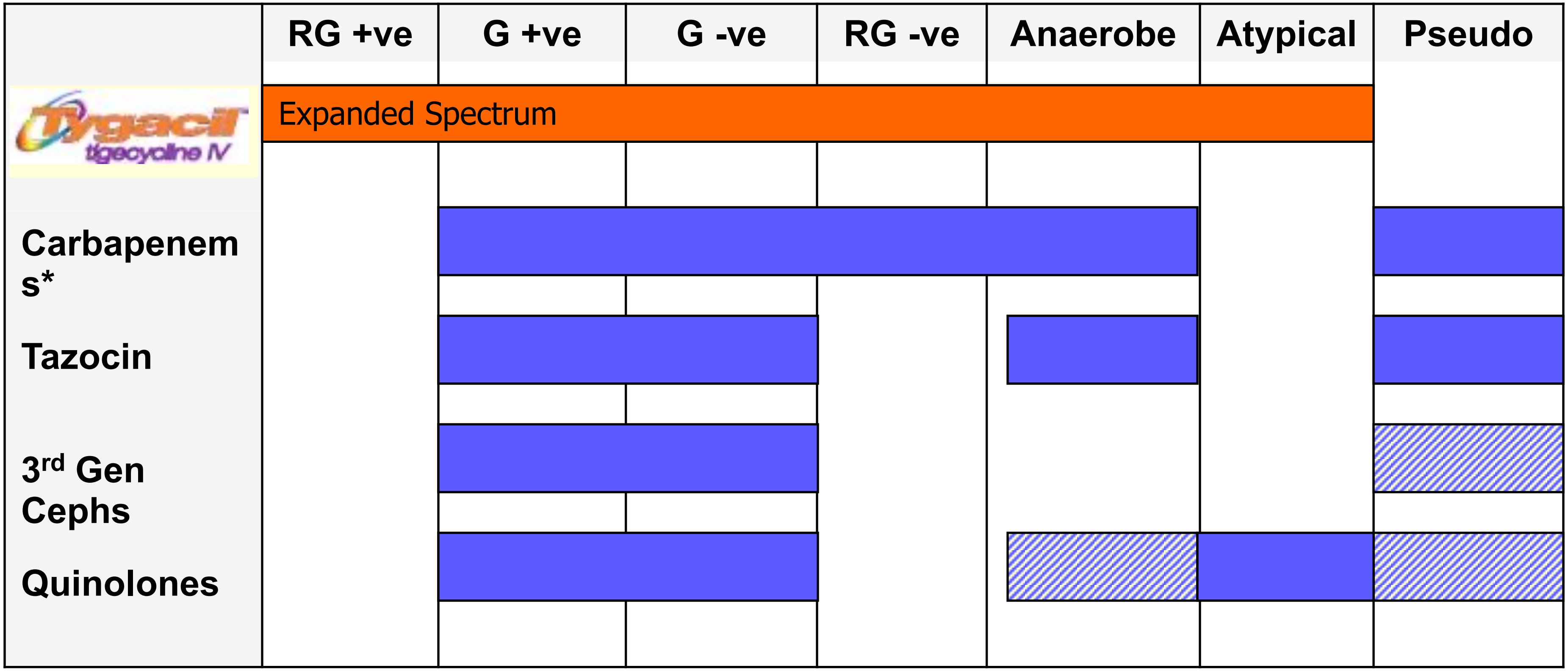
- Tetracycline, Minocycline, Doxycycline

  q6h q12h q24h
- Indications
  - Mycoplasma infection
  - Chlamydia infection
  - Rickettsial infection
    - Scrub typhus (Tsutsugamushi disease)
    - Q fever
  - Effective for *Vibrio* spp.
  - Leptospirosis

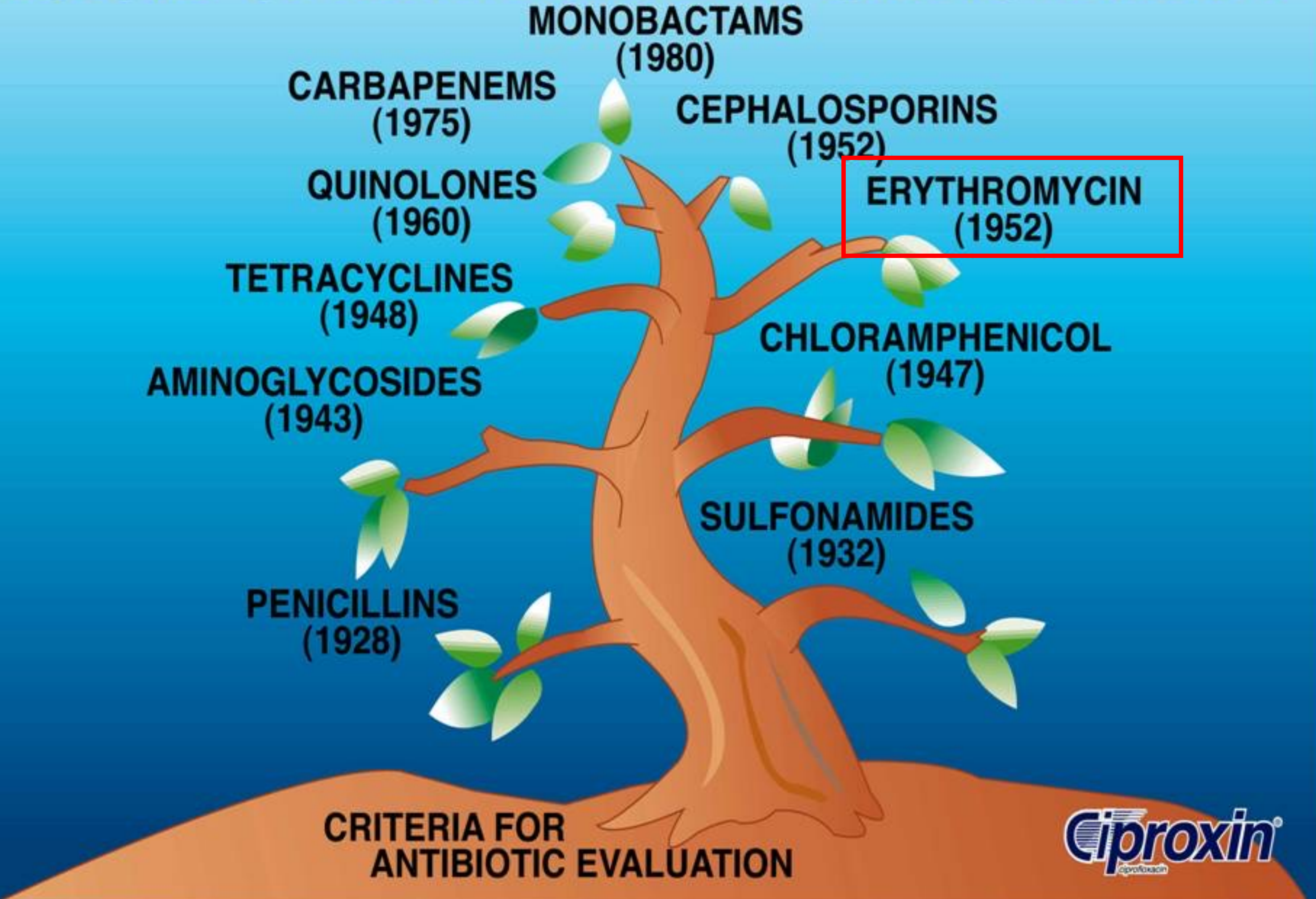
Tigecycline: Spectrum

- MDR pathogens (*MRSA, VRE, A. baumannii, ESBL-producing enterobacteriaceae*) which are resistant to other antimicrobials
- Allergy to other class antibiotics
- Polymicrobial infections
- Salmonellosis
- Rapid-growing mycobacterium

Tigecycline

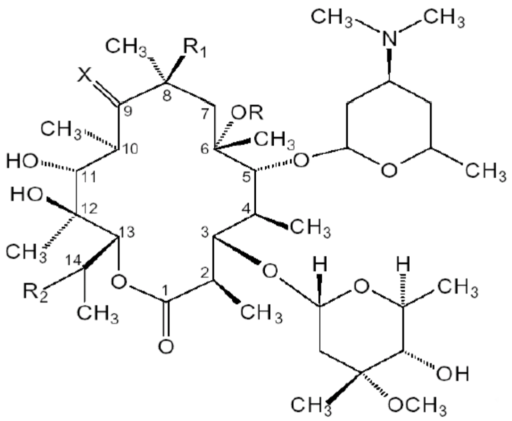


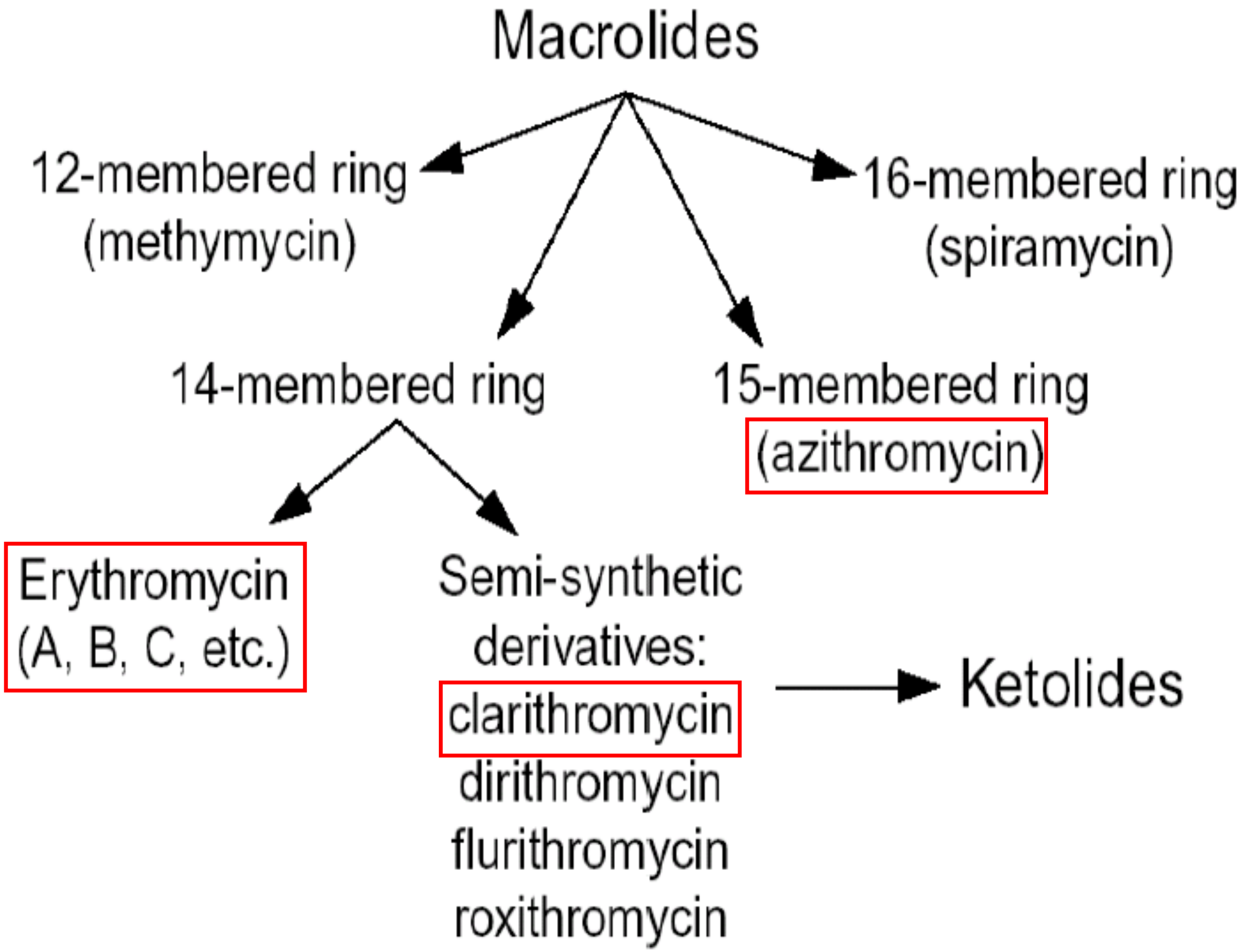
HISTORY OF ANTIMICROBIAL CHEMOTHERAPY



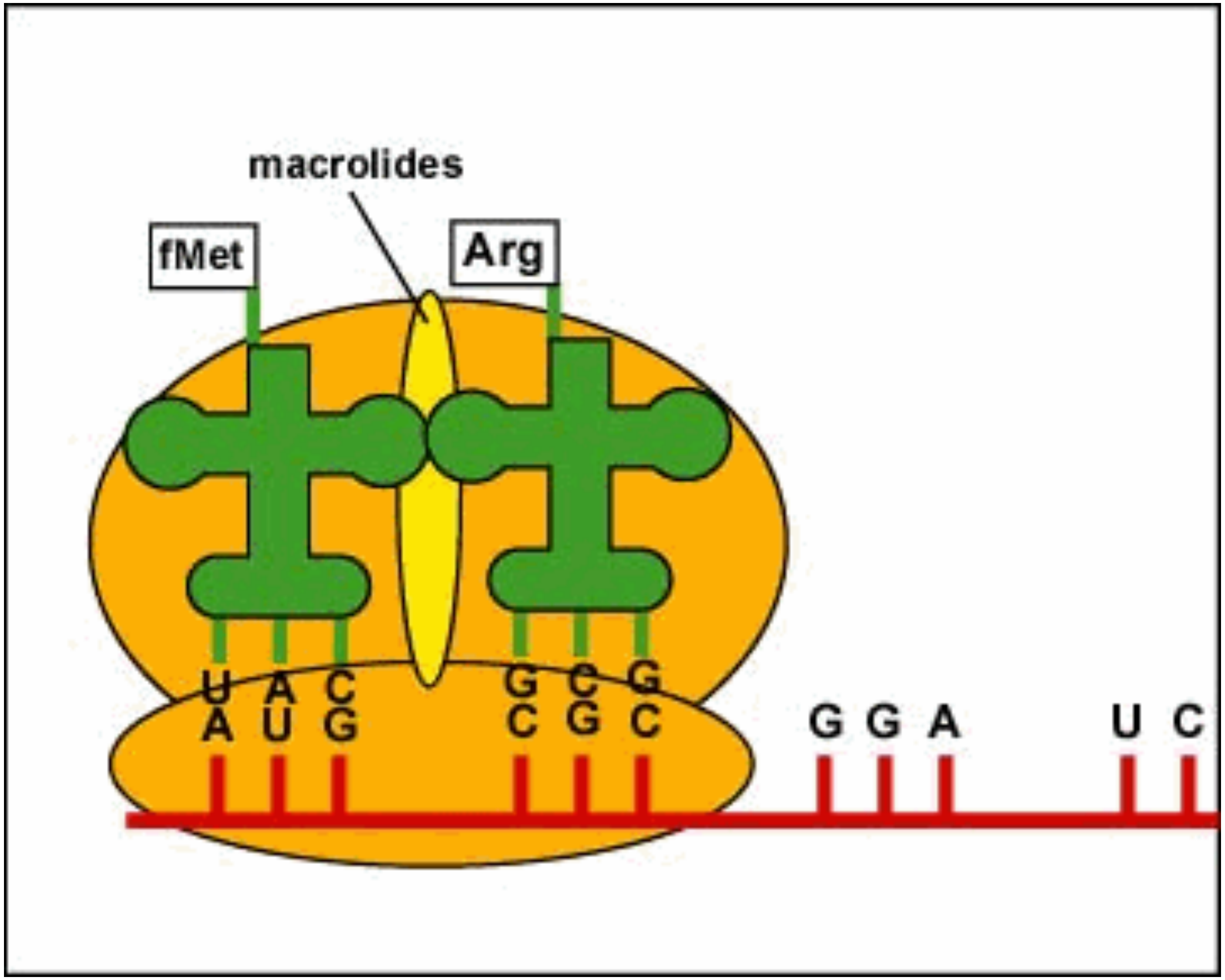
Ciproxin
ciprofloxacin

Marcolides




Macrolides
12-membered ring
(methymycin)
16-membered ring
(spiramycin)
14-membered ring
15-membered ring
(azithromycin)
Erythromycin
(A, B, C, etc.)
Semi-synthetic
derivatives:
clarithromycin
dirithromycin
flurithromycin
roxithromycin
Ketolides

Macrolide mechanism (1)



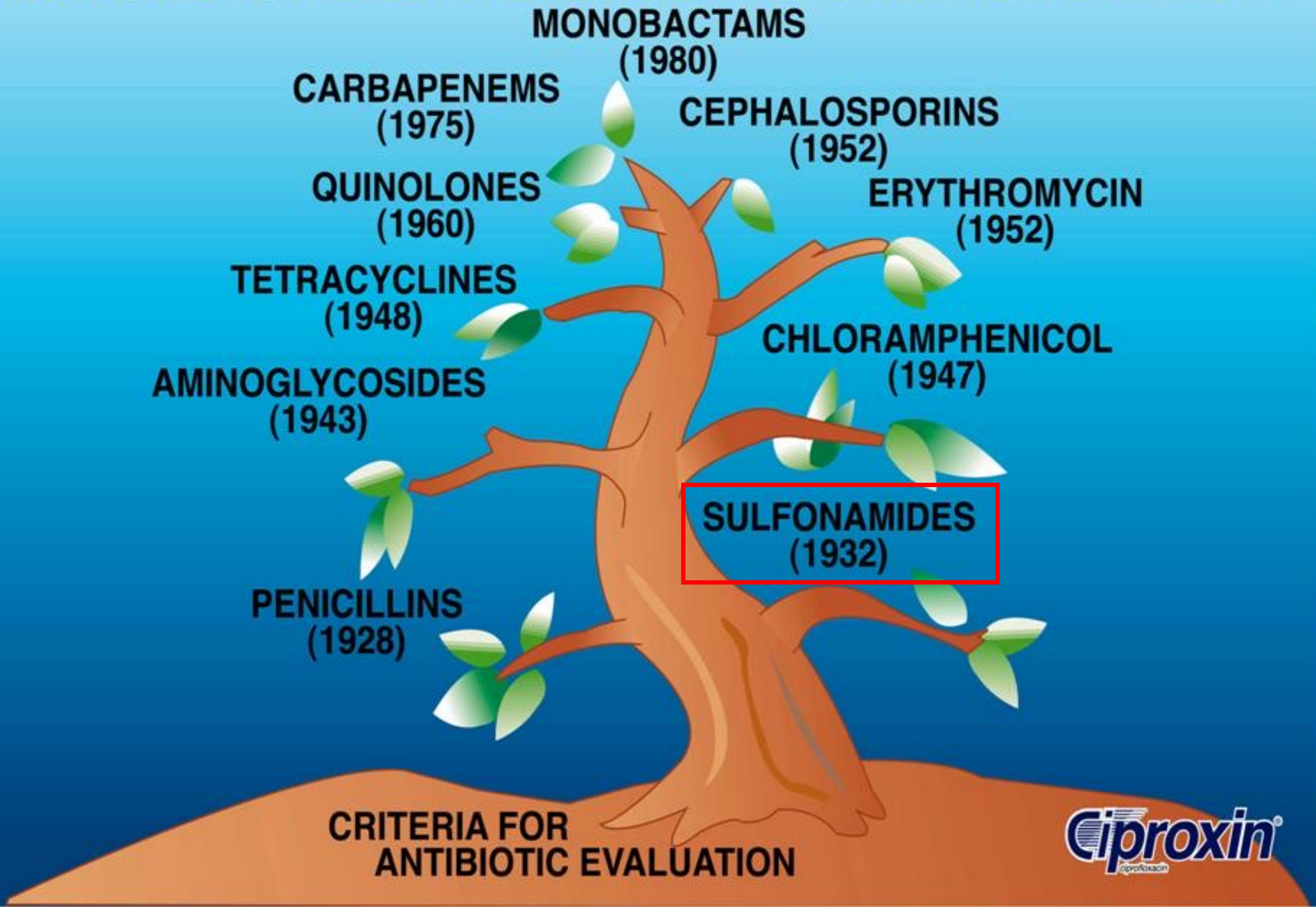
Erythromycin

- From *Streptomyces erythreus*: problems with acid lability, narrow spectrum, poor GI intolerance, short elimination half-life
- Mechanisim: binds to bacterial 23S ribosomal RNA of the 50S subunit; Protein chain elongation is inhibited
- New macrolide: clarithromycin, azithromycin
  - Broader spectrum of activity
  - Better bioavailability, better tissue penetration, prolonged half-lives
  - Improved tolerability, especially GI side effect

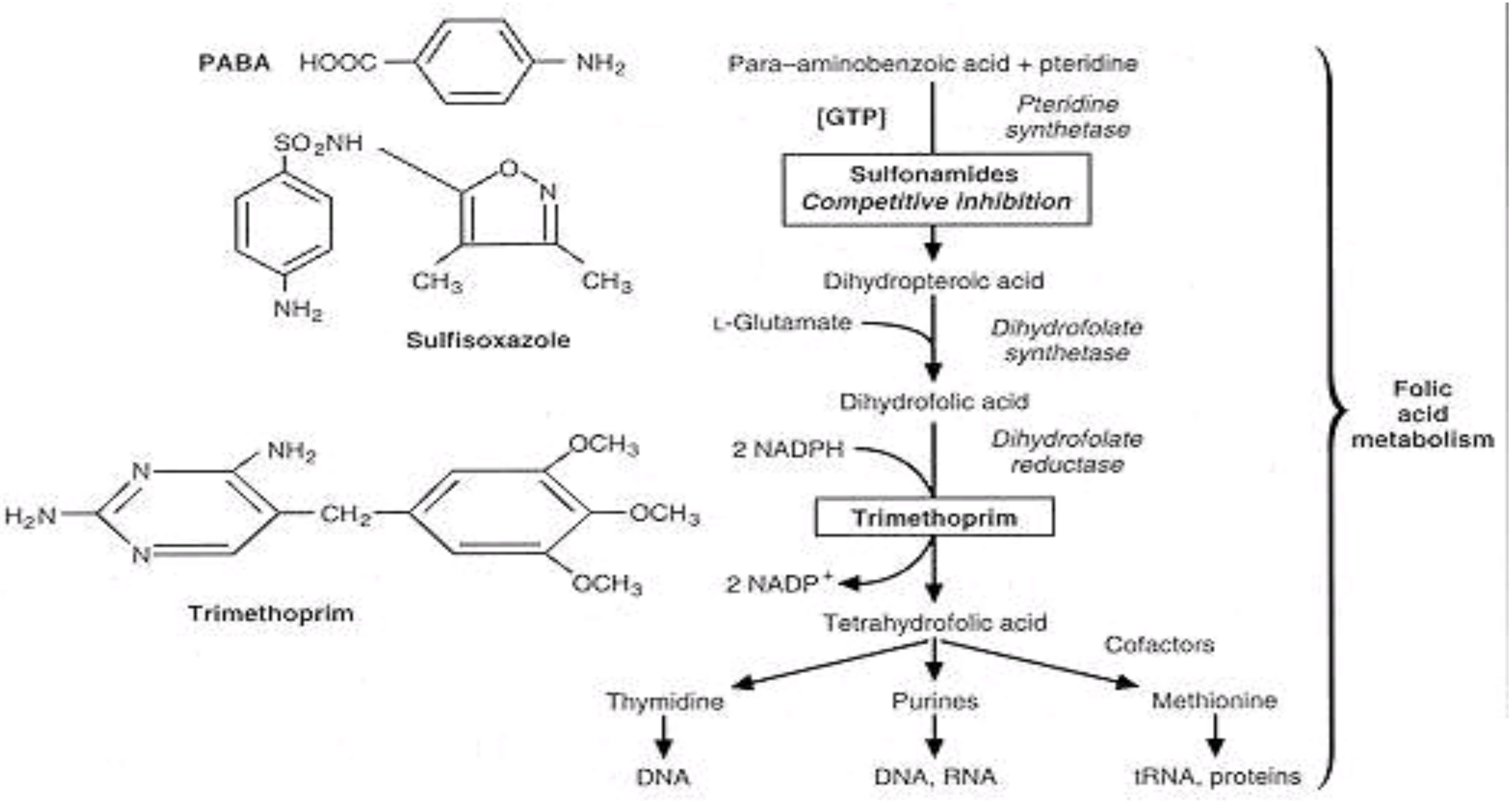
Macrolide spectrum of Activity

- G (+) Aerobes
  - Clarithro>Erythro>Azithro
- G(-) Aerobes
  - Azithro>Clarithro>Erythro
  - Do not have activity against any *Enterobacteriaceae*
- Anaerobes: upper airway anaerobes
- Atypical Bacteria
- Other Bacteria
  - MAC, Treponema pallidum, Campylobacter, Borrelia, Bordetella, Brucella. Pasteurella

HISTORY OF ANTIMICROBIAL CHEMOTHERAPY



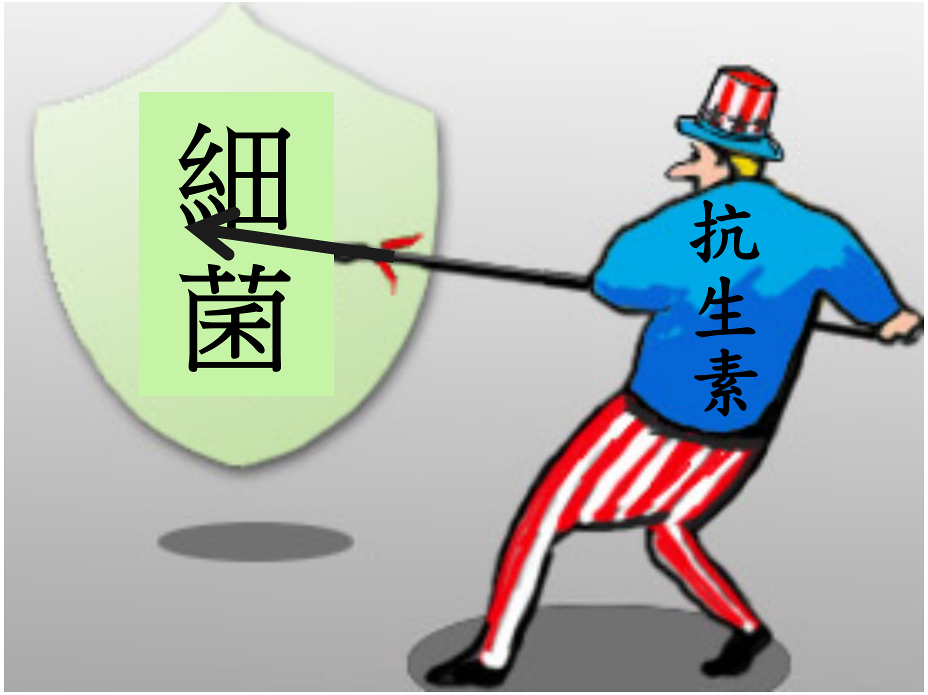
Sulfa drugs: mechanism



Sulfa drugs

- Sulfamethoxazole + Trimethoprim (Co-trimoxazole) (Baktar, Septrim)
- Clinical applications
  - Uncomplicated UTI
  - *Pneumocystis jirovecii* infection
  - Nocardial infections
  - Toxoplasmosis
  - Nosocomial infections due to Stenotrophomonas
  - Traveler diarrhea
  - Salmonellosis

抗生素與病原菌 – 矛與盾



Antibiotics vs Microorganism

- Antibiotic resistance keeps evolving.
  - ***Life will find its way out!***
- New drugs are continually being introduced to combat evolving patterns of resistance.

Thanks for your attention !!